

UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF MASSACHUSETTS

JOHN HANCOCK LIFE INSURANCE  
COMPANY, JOHN HANCOCK  
VARIABLE LIFE INSURANCE  
COMPANY and MANULIFE  
INSURANCE COMPANY,

Plaintiffs,

v.

ABBOTT LABORATORIES,

Defendant.

CIVIL ACTION NO. 05-11150-DPW

**ABBOTT'S CORRECTED DEPOSITION DESIGNATIONS FOR PERRY NISEN**

Defendant Abbott Laboratories ("Abbott") respectfully submits the attached corrected deposition designations for the February 16, 2007 deposition of Perry Nisen, former Divisional Vice-President, Oncology Development (ABT-518)

.

Dated: February 21, 2008

Respectfully submitted,

ABBOTT LABORATORIES

By:     /s/ Eric J. Lorenzini      
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**CERTIFICATE OF SERVICE**

I hereby certify that this document(s) filed through the ECF system will be sent electronically to the registered participants as identified on the Notice of Electronic Filing (NEF) and paper copies will be sent to those indicated as non registered participants on February 21, 2008.

Date: February 21, 2008.

/s/ Ozge Guzelsu

## Perry Nisen Deposition Designations

| Depo Date  | Witness      | Hancock Designation | Abbott Counter Designation | Abbott Designation | Deposition Exhibit | Plaintiff Exhibit | Defendant Exhibit |
|------------|--------------|---------------------|----------------------------|--------------------|--------------------|-------------------|-------------------|
| 11/22/2006 | Nisen, Perry |                     |                            | 9:12 - 9:16        |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 12:15 - 13:12      |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 16:5 - 18:7        |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 18:10 - 19:12      |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 19:16 - 19:19      |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 20:18 - 22:5       |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 22:11 - 23:2       |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 27:17 - 27:22      |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 30:7 - 30:23       |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 32:1 - 32:4        |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 37:8 - 39:19       |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 39:23 - 40:22      |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 41:20 - 42:7       |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 50:1 - 50:4        | Nisen 2            |                   | 825               |
| 11/22/2006 | Nisen, Perry |                     |                            | 51:20 - 52:14      |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 57:24 - 62:19      |                    |                   |                   |
| 11/22/2006 | Nisen, Perry |                     |                            | 63:19 - 65:5       |                    |                   |                   |

| <b>Depo Date</b> | <b>Witness</b> | <b>Hancock Designation</b> | <b>Abbott Counter Designation</b> | <b>Abbott Designation</b> | <b>Deposition Exhibit</b> | <b>Plaintiff Exhibit</b> | <b>Defendant Exhibit</b> |
|------------------|----------------|----------------------------|-----------------------------------|---------------------------|---------------------------|--------------------------|--------------------------|
| 11/22/2006       | Nisen, Perry   |                            |                                   | 67:19 - 69:23             |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 93:17 - 94:10             |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 97:2 - 97:14              |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 101:4 - 103:1             |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 110:18 - 113:2            | Nisen 5                   |                          | 826                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 114:5 - 117:3             |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 119:2 - 120:1             |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 138:4 - 138:14            |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 149:21 - 150:1            | Nisen 10                  |                          | 827                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 165:20 - 166:17           |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 184:8 - 184:15            |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 185:6 - 185:11            |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 190:18 - 191:12           | Nisen 11                  |                          | 828                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 217:1- 218:14             |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 219:2 - 219:11            |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 244:16 - 247:6            |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 319:2- 320:11             |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 337:2-337:5               | Nisen 31                  |                          | D_GI                     |

| <b>Depo Date</b> | <b>Witness</b> | <b>Hancock Designation</b> | <b>Abbott Counter Designation</b> | <b>Abbott Designation</b> | <b>Deposition Exhibit</b> | <b>Plaintiff Exhibit</b> | <b>Defendant Exhibit</b> |
|------------------|----------------|----------------------------|-----------------------------------|---------------------------|---------------------------|--------------------------|--------------------------|
| 11/22/2006       | Nisen, Perry   |                            |                                   | 337:22-340:22             | 31                        |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 341:1-344:18              | 32                        |                          | 829                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 360:7-361:10              |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 372:21-373:18             | 37                        |                          | 830                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 386:6-387:16              |                           |                          |                          |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 389:14-391:9              | 10                        |                          | 827                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 391:10-396:5              | 38                        |                          | 831                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 396:8-397:16              | 39                        |                          | 832                      |
| 11/22/2006       | Nisen, Perry   |                            |                                   | 398:4-405:7               | 40                        |                          | 833                      |

## **Color Key to Deposition Designations**

 **Designation by Plaintiffs**

 **Counter Designation by Defendants**

 **Designation by Defendants**

CONFIDENTIAL

1

1 IN THE UNITED STATES DISTRICT COURT  
2 FOR THE DISTRICT OF MASSACHUSETTS

3 - - -

4 JOHN HANCOCK LIFE : CIVIL ACTION  
INSURANCE COMPANY, :  
5 JOHN HANCOCK VARIABLE :  
LIFE INSURANCE COMPANY, :  
6 and MANULIFE INSURANCE :  
COMPANY (f/k/a INVESTORS:  
7 PARTNER INSURANCE :  
COMPANY), :

8 Plaintiffs,:

V. :

9 :

ABBOTT LABORATORIES, :

10 Defendant. : NO. 05-11150-DPW

11 - - -

12 November 22, 2006

13 - - -

14 CONFIDENTIAL

15 - - -

16 Videotaped deposition of PERRY  
NISEN, M.D., Ph.D., held in the offices  
17 of Morgan Lewis, LLP, 18th Floor, 1701  
Market Street, Philadelphia, Pennsylvania  
18 19103, commencing at 9:05 a.m., on the  
above date, before Denise D. Bach, a  
19 Federally Approved Registered  
Professional Reporter and a Certified  
20 Shorthand Reporter.

- - -

21

22 ESQUIRE DEPOSITION SERVICES  
Four Penn Center, Suite 1210  
23 1600 John F. Kennedy Boulevard  
Philadelphia, Pennsylvania 19103  
24 (215) 988-9191



CONFIDENTIAL

2

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14

JASON HOFFMAN, Videographer

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1 will be noted on the stenographic  
2 record. The court reporter will  
3 now swear in the witness.

4 - - -

5 PERRY NISEN, M.D., Ph.D.,  
6 having been first duly sworn, was  
7 examined and testified as follows:

8 - - -

9 EXAMINATION

10 - - -

11 BY MR. DAVIS:

12 Q. Good morning. Would you  
13 state your name for the record, please?

14 A. Perry Nisen.

15 Q. You're a doctor?

16 A. Yes.

17 Q. Dr. Nisen, my name is Brian  
18 Davis. I represent John Hancock and the  
19 other plaintiffs in this action in  
20 federal court in Boston. I'm going to be  
21 asking you a series of questions here  
22 today.

23 You understand that you're  
24 under oath?

1 again, we'll try to accommodate you as  
2 soon as possible thereafter.

3 Dr. Nisen, where do you  
4 live?

5 A. I live in Wynnewood,  
6 Pennsylvania.

7 Q. What is the street address?

8 A. 611 Argyle Circle,  
9 Wynnewood. That's venue 19096.

10 Q. How long have you lived  
11 there?

12 A. I've lived there for  
13 14 months.

14 Q. Where do you work?

15 A. I work at GlaxoSmithKline.

16 Q. What position do you hold at  
17 Glaxo?

18 A. I'm senior vice president,  
19 clinical pharmacology and discovery  
20 medicine.

21 Q. I'm sorry, would you repeat  
22 your title?

23 A. Senior vice president,  
24 clinical pharmacology and discovery

1 medicine.

2 Q. You previously worked at

3 Abbott Laboratories?

4 A. Correct.

5 Q. When did you leave Abbott?

6 A. I left there in -- two years

7 ago July. So about 25 months.

8 Q. So you left in July of 2004?

9 A. 2000 -- yes.

10 Q. It was two years ago this

11 past July?

12 A. Correct. June, July.

13 Q. Why did you leave Abbott?

14 A. I had a new opportunity at

15 GlaxoSmithKline.

16 Q. When did you start with

17 GlaxoSmithKline?

18 A. A few weeks after leaving

19 Abbott.

20 Q. Have you held any other

21 positions at GlaxoSmithKline other than

22 your current position?

23 A. No.

24 Q. Briefly, what are your

1 resolved?

2 A. I was dropped from the  
3 complaint. I don't know the legal term  
4 for that, though.

5 Q. Would you give me a brief  
6 description of your educational  
7 background, please?

8 A. I have a Bachelor's degree  
9 from Stanford, a Master's medical -- M.D.  
10 degree and Ph.D. degree from Albert  
11 Einstein College of Medicine. I have  
12 residency training in pediatrics and  
13 subspecialty training in pediatric  
14 hematology/oncology. My Ph.D. is in  
15 molecular biology.

16 I'm board certified in  
17 pediatrics, pediatric hematology/oncology,  
18 although I haven't renewed those boards.  
19 And I was a medical school professor and  
20 had -- was a full professor and had  
21 endowed chair at University of Texas  
22 Southwestern Medical School before  
23 joining Abbott.

24 Q. When did you obtain your BA?

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1 A. My?

2 Q. Your Bachelor's.

3 A. My Bachelor's, in 1976, '77.

4 Q. I'm sorry, was that a B -- a

5 Bachelor of Science or Bachelor --

6 A. Yes, Bachelor of Science.

7 Q. And you -- where did -- when

8 did you obtain your M.D.?

9 A. Five years later at Albert

10 Einstein College of Medicine in New York.

11 Q. So approximately '82?

12 A. Yes.

13 Q. And then you obtained a

14 Ph.D. at some later point in time. When

15 did you obtain your Ph.D.?

16 A. I obtained both degrees at

17 the same time from the same school. It

18 was a combined M.D./Ph.D. program.

19 Q. And for some period of time,

20 you practiced medicine?

21 A. Yes.

22 Q. When?

23 A. I practiced medicine through

24 residency and as a faculty member until I

1 left UT Southwestern -- I'm going to have  
2 trouble. I -- I don't have my CV in  
3 front of me, but I practiced for  
4 approximately -- I was on faculty for  
5 about -- I guess at least ten years. And  
6 I maintained and still maintain a medical  
7 license.

8 Q. Which state?

9 A. Currently in Pennsylvania.

10 Q. When you practiced medicine,  
11 where did you practice?

12 A. I practiced in New York for  
13 a period of time at Schneider Children's  
14 Hospital and Columbia-Presbyterian  
15 Medical Center, and then I practiced at  
16 University of Texas Southwestern Medical  
17 Center in Dallas.

18 Q. You said you -- you actually  
19 were a medical school professor --

20 A. Correct.

21 Q. -- at the University of  
22 Texas?

23 A. Correct.

24 Q. Teaching what?

1 A. In the department of  
2 pediatrics, clinically, and genetics and  
3 development in the basic sciences.

4 Q. You left that position to  
5 join Abbott Laboratories?

6 A. Correct.

7 Q. What year was that? As best  
8 you recall.

9 A. I've been at GSK for two  
10 years, and I was at Abbott for eight  
11 years. So over ten years ago. Around  
12 ten years ago.

13 Q. So approximately 1996?

14 A. Yeah, '96, '97, I think is  
15 the year.

16 Q. What position did you first  
17 hold when you joined Abbott?

18 A. Divisional vice president,  
19 cancer research.

20 Q. How did it come about that  
21 you went to work for Abbott at that point  
22 in time?

23 A. I was invited to give a  
24 lecture there, and after that lecture



1     there -- I had a colleague there that I  
2     worked with at Stanford many years ago.  
3     He invited me to give a lecture. After  
4     my lecture, they recruited me to this  
5     position. And I accepted it.

6           Q.   When you took the position  
7     as divisional vice president of cancer  
8     research, was that -- were you required  
9     to move to the Chicago area?

10          A.   Yes.

11          Q.   All the time that you worked  
12     at Abbott, did you work in the Chicago  
13     area?

14          A.   Yes.

15          Q.   Who was the colleague that  
16     invited you to give the lecture?

17          A.   Shing Chang.

18          Q.   What other positions did you  
19     hold at Abbott after you were divisional  
20     vice president of cancer research?

21          A.   I took on the position of  
22     divisional vice president of, I think it  
23     was called oncology development. As soon  
24     as I transitioned from drug discovery to

1 drug development, for a period, I had  
2 both accountabilities, and then, as I  
3 shifted to dominantly development, the  
4 title changed to reflect that.

5 Q. Were you divisional vice  
6 president of oncology development when  
7 you left Abbott?

8 A. Yes.

9 Q. So is it fair to say that  
10 when you joined Abbott as divisional vice  
11 president of cancer research, most of  
12 your responsibilities had to do with  
13 discovery?

14 A. Yes.

15 Q. And at some point in time,  
16 your -- your responsibilities changed so  
17 that you had more responsibility for  
18 development, is that right?

19 A. As the assets entered into  
20 the clinic, I followed them, given my  
21 training and experience, which was in  
22 both basic sciences and clinical  
23 medicine.

24 Q. Was one of those assets a

1 compound named ABT-518?

2 A. Yes.

3 Q. Did you work on ABT-518 when  
4 it was in the discovery phase?

5 A. Yes.

6 Q. And how many other compounds  
7 were among the assets that you helped  
8 manage from research into development?

9 A. I'll have to count. About a  
10 half a dozen.

11 Q. And can you briefly  
12 describe, again for us lay people, the  
13 difference between discovery and  
14 development as it pertains to the drug  
15 compounds?

16 A. Generally, drug discovery  
17 refers to the identification of the  
18 molecule that one then administers to  
19 people. Drug development generally  
20 refers to those studies and the conduct  
21 of studies in human beings to determine  
22 if those molecules are safe and effective  
23 in people. And there is a blurriness  
24 as an -- as an asset or a molecule goes

1 through later drug discovery and enters  
2 into the clinic.

3 THE VIDEOGRAPHER: Excuse  
4 me. Off tape, 9:19.

5 (Whereupon, a discussion was  
6 held off the record.)

7 THE VIDEOGRAPHER: Stand by,  
8 please.

9 Back on the record, 9:21.

10 BY MR. DAVIS:

11 Q. Dr. Nisen, have you ever  
12 testified under oath, other than the  
13 occasion when you were deposed?

14 A. Yes.

15 Q. Okay. On what other  
16 occasions have you testified under oath?

17 A. When I was a house officer  
18 at Columbia-Presbyterian, I testified in  
19 a murder case, actually, of a child who I  
20 took care of in the emergency room.

21 Q. Was that a trial?

22 A. Yeah.

23 Q. Have you testified in any  
24 other trials?

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1 regulatory purposes that included various  
2 clinical dossiers and reports and  
3 summaries of material. I don't remember  
4 if there was a specific preclinical  
5 database or not.

6 Q. Were the -- were there teams  
7 at Abbott that were devoted to  
8 development of specific compounds?

9 A. Yes.

10 Q. So, for example, was there  
11 an ABT-518 team?

12 A. Yes.

13 Q. And if I refer to it as 518,  
14 you'll understand that I'm referring to  
15 ABT-518, is that fair?

16 A. Yes.

17 Q. Who was on the 518 team?

18 A. To the best of my  
19 recollection, Azmi Nabulsi, a physician  
20 lead, Diane D'Amico, as a project  
21 manager, or clinic -- I guess clinical  
22 operations activities.

23 Q. Um-hmm.

24 A. And there were other

1 program and I can't remember exactly who  
2 was involved when.

3 Q. Would Dr. Nabulsi have been  
4 responsible for helping to oversee any  
5 clinical trials of 518?

6 A. Yes, probably.

7 Q. Were you a member of the 518  
8 development team?

9 A. I was in charge of overall  
10 development of all of the oncology  
11 assets. So to the extent that 518 was an  
12 oncology asset, I was involved as the  
13 head of that program. I was not -- I  
14 didn't lead the project team meetings,  
15 for example.

16 Q. Did you attend project team  
17 meetings?

18 A. Not in general, to my  
19 recollection.

20 Q. On occasion?

21 A. Possibly. I don't  
22 specifically remember. But not in  
23 general, to my recollection.

24 Q. Were there 518 team records

1 Q. In your capacity as  
2 divisional vice president of oncology  
3 development, to whom did you report?

4 A. John Leonard.

5 Q. What was his position?

6 A. I believe his title was vice  
7 president, development.

8 Q. How frequently did you  
9 report to Dr. -- it's Dr. Leonard,  
10 correct?

11 A. Do you mean how often did we  
12 meet?

13 Q. Well, is Mr. Leonard a  
14 doctor, to your knowledge?

15 A. Yes.

16 Q. How frequently did you meet  
17 or report to him regarding the status of  
18 projects that you were supervising?

19 MR. LORENZINI: Objection.

20 You can answer.

21 BY MR. DAVIS:

22 Q. You can -- if he objects,  
23 unless he instructs you otherwise, you  
24 can go ahead and answer the question.

1 Q. Was one of the assets that  
2 was reviewed in the course of that  
3 meeting, to the best of your  
4 recollection, 518?

5 A. Possibly, but I don't  
6 remember the specifics of what we talked  
7 about.

8 Q. You were aware before the  
9 research funding agreement between  
10 Hancock and Abbott was signed that such a  
11 deal was being negotiated?

12 A. Yes.

13 Q. How were you made aware of  
14 that fact?

15 A. I had, to my recollection,  
16 conversations with some of the business  
17 development people. Initially the head  
18 of R&D finance, whose name, Steve, I  
19 don't remember.

20 Q. Mr. Cohen?

21 A. Cohen, Steve Cohen, and Phil  
22 Deemer.

23 Q. Do you recall when it was  
24 approximately that you first became aware



1 of the -- of a potential deal between  
2 Hancock and Abbott?

3 A. No.

4 Q. Were you asked by Mr. Deemer  
5 or Mr. Cohen or anyone else in Abbott to  
6 provide any assistance or support in  
7 helping to make that deal happen?

8 A. I was asked to provide  
9 information about the assets, the  
10 oncology assets.

11 Q. What information were you  
12 asked to provide?

13 A. To my recollection, what we  
14 knew about it, what the target was, what  
15 the attributes of the asset were, how we  
16 were planning to develop it, what its  
17 development status was.

18 Q. Were -- was there more than  
19 one oncology asset that you reviewed or  
20 discussed with Mr. Deemer and Mr. Cohen  
21 in this context?

22 A. Yes.

23 Q. Which assets? Which  
24 compounds, if I can call them that?

1 A. We -- we likely reviewed all  
2 of the assets in or near clinical  
3 development in oncology at the time.

4 Q. Do you recall the numbers or  
5 designations for those particular assets?

6 A. I can do my best.

7 Q. That's all I can ask.

8 A. There was an endothelin  
9 receptor antagonist called ABT-627.  
10 There was probably an antimitotic  
11 compound called ABT-751. There might  
12 have been an angiogenesis inhibitor  
13 called ABT-510. Probably ABT-518 that  
14 we're talking about. And I think we had  
15 already terminated another molecule,  
16 which was ABT-839, which was a farnesyl  
17 transferase inhibitor.

18 I believe those to be the  
19 main ones.

20 Q. The ABT-627, was that also  
21 known as Xinlay?

22 A. Yes.

23 Q. And are you aware that some  
24 of the compounds that you discussed with

1 Mr. Deemer and Mr. Cohen ultimately were  
2 included in the basket of compounds that  
3 were encompassed by the agreement with  
4 Hancock?

5 A. Yes.

6 Q. And you knew that 518, for  
7 example, was going to be among the  
8 compounds included in the basket, is that  
9 correct?

10 A. I think so, yes.

11 Q. Among the activities that  
12 you engaged in before the agreement with  
13 Hancock was signed, did you assist in  
14 developing descriptive memoranda for any  
15 of the compounds?

16 MR. LORENZINI: Objection.

17 THE WITNESS: I don't  
18 remember specific descriptive  
19 memoranda, but I do remember being  
20 involved in providing information  
21 and data likely generated by  
22 others.

23 MR. DAVIS: Let's mark this,  
24 please, as Exhibit Number 1.

Nisen, Perry (Linked) 11/22/2006 9:05:00 AM

1 (Exhibit No. Nisen-1,  
2 Descriptive Memorandum, May 2000,  
3 Bates ABBT246447/246454, was  
4 marked for identification.)

5 BY MR. DAVIS:

6 Q. Dr. Nisen, you have what has  
7 been marked as Exhibit Number 1 at your  
8 deposition. I'm going to ask you to look  
9 at that document for a moment and tell me  
10 if you've seen it before, please.

11 A. I saw it yesterday with Eric  
12 Lorenzini.

13 Q. Prior to seeing it with Mr.  
14 Lorenzini, reviewing it with him  
15 yesterday, had you seen this document  
16 before?

17 A. I don't specifically  
18 remember whether I saw this document or  
19 not.

20 Q. Do you recall whether you  
21 assisted in any way in the development of  
22 any descriptive memoranda with respect to  
23 any oncology compounds for purposes of  
24 the Hancock deal?

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1 A. I remember that I was asked  
2 to provide information about the assets  
3 that led -- I remember that I -- I  
4 contributed that information, various  
5 information, various other documents and  
6 various other information that summarized  
7 information about the assets.

8 I don't recall this  
9 particular document.

10 Q. The information that you  
11 provided in response to the request, did  
12 you create anything, did you create any  
13 new written documents, for example, or  
14 did you simply provide copies of existing  
15 documents?

16 A. I don't remember.

17 Q. And you, as you sit here  
18 today, do you know who created a  
19 descriptive memoranda for ABT-518, for  
20 example?

21 A. No.

22 Q. Do you recall reviewing  
23 drafts of descriptive memoranda for  
24 ABT-518?

1 (Exhibit No. Nisen-2,  
2 ABT-518 February 2001 Document,  
3 Bates ABBT0000343/0000348, was  
4 marked for identification.)

5 BY MR. DAVIS:

6 Q. Dr. Nisen, you have in front  
7 of you what has been marked as Exhibit 2.  
8 Would you tell me, please, if you've seen  
9 this document before?

10 A. I believe I saw this  
11 yesterday with Eric Lorenzini.

12 Q. Prior to reviewing this  
13 document with Mr. Lorenzini, had you seen  
14 this document before?

15 A. I don't remember the  
16 specific document.

17 Q. Had you seen documents in  
18 this format before?

19 A. Not that I can exactly  
20 remember. The challenge I'm having, to  
21 be clear, is five years ago, different  
22 company, two years intensively involved  
23 with this new company. It's very  
24 difficult for me to recall, or it's

1 impossible for me to recall explicitly  
2 certain documents of certain sorts.

3 Q. Well, we're going to look at  
4 a lot of documents here today, Doctor,  
5 and so I'm --

6 A. I'm going to do my best.

7 Q. -- I'm going to ask you as  
8 best you recall --

9 A. Yeah.

10 Q. Okay.  
11 -- in each instance to tell  
12 me whether you've seen the documents  
13 before or whether you can recall  
14 reviewing either those specific documents  
15 or documents of that type.

16 I'll represent to you that  
17 this is a document produced to us by  
18 Abbott in this matter.

19 A. Um-hmm.

20 Q. That appears to be some sort  
21 of monthly report pertaining to ABT-518.  
22 And let me ask you whether, is it your --  
23 is it consistent with your recollection  
24 that when you worked at Abbott, there

1 were monthly reports of some type  
2 generated within Abbott specific to  
3 particular compounds?  
4 A. I -- yes, there were -- yes,  
5 I remember that there were regular  
6 summaries of assets following certain  
7 kinds of templates. I don't remember  
8 this specific one. I don't remember if  
9 this was the one used monthly or where it  
10 was used or to whom it might have been  
11 distributed, nor do I remember this  
12 particular document, although, I do  
13 recall reviewing documents of various  
14 sorts like it.

15 Q. Do you recall reviewing some  
16 sort of monthly reports concerning the  
17 compounds for which you were responsible?

18 MR. LORENZINI: Objection.

19 THE WITNESS: Could you be  
20 more specific?

21 BY MR. DAVIS:

22 Q. Sure.

23 In your capacity as vice  
24 president of -- the official title was



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1 in -- there were these decision  
2 trees analysis -- decision tree analyses  
3 of the portfolio. I remember more  
4 involvement around that.  
5 I don't remember who might  
6 have put together sort of this monthly,  
7 if there -- a monthly status update  
8 report. I'm sure there was a group doing  
9 that. I'm not sure. There was a likely  
10 group doing that. I cannot recall the  
11 details of who did it or how they did it  
12 or what the form was or to whom they sent  
13 it.

14 Q. Would you look at Exhibit 2  
15 for a moment?

16 A. Yes.

17 Q. I want to ask you some  
18 questions about the actual subject  
19 matter --

20 A. Okay.

21 Q. -- that's identified in  
22 Exhibit 2. First with some basic  
23 questions.

24 What was or what is ABT-518?

1 A. It's a matrix meta --  
2 metalloproteinase inhibitor. A -- matrix  
3 metalloproteinases are enzymes in the  
4 body that affect a lot of processes,  
5 including invasion -- the ability of  
6 cancer cells to invade and spread. And  
7 this molecule was selective for two of  
8 those metalloproteinases that seem to be  
9 particularly important in the invasion  
10 and spread of cancer cells.

11 Q. Is it fair to say that  
12 ABT-518 was a compound that Abbott  
13 thought might inhibit tumor growth in  
14 someone?

15 A. Particularly metastasis or  
16 spread.

17 Q. And that was the reason why  
18 Abbott was interested in ABT-518, is that  
19 correct?

20 A. Yes.

21 Q. And you said it's a  
22 metalloproteinase inhibitor. Is that  
23 group of compounds sometimes referred to  
24 as MMPs?

1 A. Yes.

2 Q. So ABT-518 was an MMPI?

3 A. Yes.

4 Q. Did Abbott have other MMPI

5 compounds under development while you

6 worked there at any point in time?

7 A. No. We had -- there was a

8 long-term drug discovery program leading

9 to the generation of MMPI molecules for

10 clinical investigation. 518 was the

11 molecule that I remember that we entered

12 into the clinic. We had other

13 precandidates or candidates that fell

14 down along the way because of either

15 toxicologic findings or other

16 information. This is the molecule I

17 remember we entered to the clinic.

18 Q. Was there something

19 particular or particular characteristics

20 that caused you to enter this compound

21 into clinical trials as opposed to

22 others?

23 A. Yes.

24 Q. What were they?

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1       A.    So we were impressed by the  
2   selectivity of this inhibitor in contrast  
3   to many of the other MMPs in  
4   development. The other ones more -- in  
5   more advanced stages of development were  
6   more pan inhibitors across that family of  
7   enzymes, and we thought that we might be  
8   able to achieve the benefit of clinical  
9   efficacy in cancer, targeting just those  
10   two enzymes and not have the liabilities  
11   with respect to safety that the pan  
12   inhibitors had, because they were causing  
13   joint toxicities and joint pain, so we  
14   thought it was a problem and limited the  
15   ability to administer those.

16       We were also impressed, to  
17   my recollection, with the pharmaceutical  
18   properties of the molecule was very  
19   potent and it had good bioavailability  
20   and good pharmacokinetics, meaning its  
21   exposure in the body. So we thought it  
22   had good drug-like qualities in addition  
23   to being a target that we thought and  
24   others obviously thought was an

1 interesting target for intervention for  
2 cancer.

3 Q. I'm trying to break down  
4 some of what you said --

5 A. Yes.

6 Q. -- so that ultimately  
7 non-physicians reading this material  
8 might understand it.

9 You said that you thought  
10 that you were impressed by the  
11 selectivity of it?

12 A. Yes.

13 Q. Meaning that you understood  
14 that 518, as best you could tell,  
15 targeted specific enzymes, is that  
16 correct?

17 A. Yes.

18 Q. Two in particular?

19 A. Yes.

20 Q. And you thought that the  
21 advantage to that was that by targeting  
22 just two enzymes, the -- some of the  
23 disadvantages that might have been  
24 observed in other MMPI candidates, for

1 example, joint pain, might not be present  
2 or might be present in a lesser amount if  
3 someone used 518?

4 A. Correct.

5 Q. In addition, I think you  
6 made some reference to that you were  
7 impressed by the pharmaceutical  
8 properties of it, that you thought it  
9 was, excuse me, I don't have the  
10 transcript in front of me, but you  
11 thought it was more efficacious?

12 A. I said that it was more  
13 potent.

14 Q. More potent.

15 A. Meaning that less could be  
16 given to inhibit the enzyme, that you  
17 could swallow the pill and it would be  
18 absorbed into the bloodstream, what we  
19 would refer to as bioavailability.

20 There's a fire drill at  
21 10 o'clock.

22 Q. Yes. I -- I think we're  
23 entitled to sit through it, but I noticed  
24 on the way in this morning that there was

1 a sign up that there would be a fire

2 drill at 10:00 a.m.

3 A. Right.

4 Q. So I am going to assume that

5 they'll let us know if it's more than --

6 more than just the drill.

7 A. So you are not required to

8 leave the building?

9 Q. Unless and until we're told,

10 we're -- we're going to stay here.

11 A. Okay.

12 Q. Although you're free to

13 leave if you wish to. I'm -- make sure

14 that I'm not instructing you to stay

15 here.

16 A. I'm enthusiastic that --

17 Q. My luck, the tape would be

18 the one thing that survived.

19 Okay. You mentioned that

20 you thought it was more --

21 A. Potent, bioavailable, so

22 that it could be absorbed and stayed in

23 the bloodstream for a period of time, so

24 we thought those were important

1 attributes.

2 Q. Did you think that those  
3 were attributes that would -- were not  
4 necessarily demonstrated by other MMPI  
5 compounds?

6 A. We thought this would be  
7 potentially better -- that those  
8 properties would be better than the  
9 others.

10 Q. When you say the others, you  
11 mean MMPI compounds under development by  
12 other companies?

13 A. Correct.

14 Q. And was one of those other  
15 MMPI compounds marimastat?

16 A. Yes.

17 Q. Was a -- do you recall the  
18 names of any of the other MMPI compounds  
19 that were under development by other  
20 companies?

21 A. There was tanomastat. There  
22 was a Bayer compound. There was a  
23 Bristol-Myers compound. There were  
24 probably ten or so. An Agouron molecule.



1 There were at least ten matrix  
2 metalloproteinase inhibitors in  
3 development. There was a lot of interest  
4 in the scientific oncology community in  
5 this target.

6 Q. At least as of 2001, did you  
7 believe that 518 had potential advantages  
8 over those other MMPI compounds?

9 A. Yes.

10 MR. LORENZINI: Objection.

11 BY MR. DAVIS:

12 Q. Were you -- did you ever, in  
13 your own mind, prove or disprove whether  
14 that was, in fact, the case?

15 MR. LORENZINI: Objection.

16 THE WITNESS: Could you help  
17 me -- be more specific about your  
18 question?

19 BY MR. DAVIS:

20 Q. Certainly.

21 As of 2001, you had a belief  
22 that ABT-518 might have the advantages  
23 that you described of -- over other MMPI  
24 compounds, is that correct?

1 differentiate assets at -- in  
2 early Phase I. So I don't think  
3 it's answerable in early Phase I.

4 BY MR. DAVIS:

5 Q. Well, did this compound  
6 progress beyond Phase I?

7 A. No.

8 Q. And did Abbott continue to  
9 engage in clinical development of 518 for  
10 the purpose of determining whether the  
11 beliefs that you held regarding its  
12 potential advantages were correct?

13 MR. LORENZINI: Objection.

14 THE WITNESS: Can you help  
15 me understand your question a  
16 little better?

17 BY MR. DAVIS:

18 Q. Fine.

19 At some point in time, was  
20 clinical development of 518 terminated by  
21 Abbott?

22 A. Yes.

23 Q. When was that?

24 A. I don't remember exactly,

1 but at a point after, to my recollection,  
2 after the American Society for Clinical  
3 Oncology meetings in, I believe, May, I  
4 imagine that would be 2001 then, I think  
5 the collection of data, at that point in  
6 time, with regard to several  
7 presentations of competitor molecules,  
8 really led to the decision that the  
9 likelihood of success, given the lack of  
10 success with the other multiple  
11 molecules, targeting matrix  
12 metalloproteinase inhibitors, that they  
13 were all -- the body of negative  
14 evidence, I think the tipping point, was  
15 reached largely around then.

16 Q. Would it be fair to say that  
17 Abbott decided, based on information  
18 about other competing compounds, that it  
19 did not wish to pursue further  
20 development of ABT-518?

21 MR. LORENZINI: Objection.

22 But you can answer.

23 THE WITNESS: Could you try  
24 that again?

1 BY MR. DAVIS:

2 Q. Certainly.

3 Is it fair to say that  
4 Abbott decided not to further pursue the  
5 development of ABT-518 based upon  
6 information obtained regarding other  
7 competing compounds?

8 A. I remember that that  
9 contributed to the decision.

10 Q. Was it any particular  
11 information obtained during trials of  
12 ABT-518 that caused Abbott, to your  
13 knowledge, to cease development of that  
14 compound?

15 A. My recollection was that the  
16 real turning point for the decision about  
17 developing MMPIs was dominated by what  
18 seemed like at the time the overwhelming  
19 negative clinical evidence with other  
20 molecules.

21 Q. Not --

22 A. That were more advanced than  
23 ABT-518.

24 Q. If you'd look back on Page 1

1 necessary to conduct Phase I studies.

2 When one says -- I guess I'm  
3 struggling with your point of when Phase  
4 I began. So is it -- we generally refer  
5 to the initiation of all those activities  
6 as the initiation of Phase I. We might  
7 use as a metric when the first subject is  
8 actually dosed, but it's really a small  
9 part in the continuum of activities.

10 Q. To your recollection --

11 A. So there was commitment to  
12 conduct that work necessarily --  
13 necessary to start. And I can't pick  
14 through dates of what started when and  
15 what Phase I means. And that -- there  
16 I'll have trouble to answer.

17 Q. When it says "Study will  
18 initiate October, 2000," what does that  
19 mean?

20 A. Well, I don't remember  
21 exactly what that means.

22 Q. You don't know what it means  
23 to initiate a study?

24 A. To initiate -- again, so to

1 initiate a study to me means conducting  
2 all that work coincident with starting,  
3 so drug product, toxicology, clinical --  
4 a clinical -- creation of the clinical  
5 study, the clinic -- the dossier  
6 regulatory approval, ethics review board  
7 approval.

8 So there's a constellation  
9 of events. So it's those myriad that --  
10 those myriad activities.

11 Q. To your knowledge, had  
12 Abbott elected or decided to fund a Phase  
13 I clinical trial of ABT-518 as of  
14 April 2000?

15 A. Again, I don't remember  
16 dates. My ability to recall specific  
17 dates, I can't do.

18 Q. Well, based on what you see  
19 in this document, is it your  
20 understanding that Abbott had elected or  
21 decided to fund a Phase I clinical study,  
22 at least as of this time?

23 A. Yes.

24 Q. And if you take a look a few

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1 A. No. I meant pause.

2 Q. Do you recall -- do you

3 recall some sort of directive or order

4 coming from Abbott to people working on

5 the trial that they should stop enrolling

6 patients in that trial?

7 A. I remember that there was a

8 request to pause activities. I don't

9 remember the specifics.

10 Q. Who made the decision to

11 pause activities in that trial?

12 A. I don't remember

13 specifically, but likely involved John

14 Leonard and Jeff Leiden.

15 Q. Do you recall Dr. Leonard

16 and -- I think it's Dr. Leiden -- being

17 involved in that decision?

18 A. I don't remember the

19 specifics.

20 Q. Do you recall generally that

21 they were involved in that decision?

22 MR. LORENZINI: Objection.

23 Asked and answered.

24 THE WITNESS: I don't

1 A. Yes.

2 Q. And that would include 518?

3 A. Yes.

4 Q. And you mentioned that there  
5 were concerns around accumulating body of  
6 evidence regarding MMPIs, is that  
7 correct?

8 A. Yes.

9 Q. So the decision, to your  
10 knowledge, regarding the pausing of the  
11 518 Phase I clinical trial had to do with  
12 both availability of resources to fund  
13 that development effort, but also  
14 concerns around information that was  
15 becoming known to Abbott regarding the  
16 fate or status of other MMPI compounds,  
17 is that right?

18 A. Probably. But I must be  
19 very clear, my recollections are vague  
20 and the time specifics I'm even more  
21 vague about. And I will not be able to  
22 share with you what was thought when  
23 exactly.

24 Q. But what I --



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1       A.   My -- my -- let me be clear.  
2       My -- my main recollection about concerns  
3       regarding efficacy of the class really  
4       came to a head after the -- and around  
5       that ASCO meeting in May. That's what I  
6       mostly recall. There was always  
7       accumulating data, but I do remember that  
8       a key inflection point, if you will, in  
9       terms of reasons to believe really in  
10      that, that -- after that ASCO meeting.  
11      That I mostly -- that's what I do recall.  
12      As to the funding issues,  
13      and a pause, I've expressed to you the  
14      best that I remember what happened. I  
15      really don't remember the details. I  
16      don't remember if it was a -- if there  
17      was either a decision specifically there.  
18      But I do have -- you asked me my  
19      recollection, and my recollection is a  
20      flavor of -- of concerns always around  
21      inadequate resource to do all the studies  
22      we wanted to do as a general statement,  
23      which is, I think true for everybody  
24      pursuing clinical development in every

1 company with every molecule, frankly.

2 Q. Your recollection --

3 A. Yeah.

4 Q. -- around the reasons for  
5 the pause in the Phase I clinical study  
6 involving 518 has to do with the  
7 availability of resources, correct?

8 A. That's my vague  
9 recollection. But I'm really not sure.

10 Q. And -- but also --

11 A. Very vague. So if I could  
12 frame that as --

13 Q. All you can do is give us  
14 your best recollection.

15 A. Yeah. And that's --

16 Q. That is your best  
17 recollection here today, is that correct,  
18 that that was one of the factors in the  
19 decision to pause the Phase I clinical  
20 trial for 518?

21 A. I think so.

22 Q. And also one of the factors  
23 in the decision to pause the Phase I  
24 clinical study for 518, to the best of

1 expected or probable spending?

2 A. Not really.

3 Q. Do you recall within Abbott

4 any differentiation between sort of

5 nominal spending numbers and any expected

6 or probable spending based on some sort

7 of success ratio or --

8 A. Not really.

9 Q. No?

10 Were you ever called to

11 differentiate between those two in coming

12 up with planned spending numbers within

13 Abbott?

14 A. Not to my recollection.

15 MR. DAVIS: Let's mark this,

16 please, as the next exhibit,

17 Number 5.

18 (Exhibit No. Nisen-5,

19 ABT-518 Transition Strategy, Bates

20 ABBT256634/256645, was marked for

21 identification.)

22 BY MR. DAVIS:

23 Q. Dr. Nisen, you have what has

24 been marked as Exhibit 5 at your

1 deposition. Would you look at this  
2 document for a moment and tell me if you  
3 can identify it for me?

4 A. It says a "Transition  
5 Strategy," and I have the vaguest  
6 recollection of creating something like  
7 that, but it's very, very vague. My  
8 recollection is very, very vague.

9 Q. We spoke a few moments ago,  
10 I think you testified a few moments ago  
11 about the process of transitioning a  
12 prospective compound from research or  
13 discovery to clinical development.

14 Do you recall that?

15 A. Yes.

16 Q. Does this tran -- did this  
17 transition memo, to your knowledge, play  
18 any role in the process of transitioning  
19 ABT-518 from research or discovery to  
20 clinical development?

21 A. Yes. I think it looks like  
22 it summarizes most of the coincident  
23 activities necessary.

24 Q. Did -- did you or did people

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1 working for you develop this document?

2 A. Yeah. Probably.

3 Q. And to whom was this

4 document presented or submitted?

5 A. I don't remember.

6 Q. Who, by name, as best you

7 recall, within Abbott made the decision

8 to move ABT-518 from research or

9 discovery into clinical development?

10 A. My recollection was, there

11 was a meeting called this DDC, that was

12 generally attended by Jeff Leiden, Dan

13 Norbeck, who was the head of drug

14 discovery, John Leonard, and a few

15 others, where approval was given that the

16 team had successfully achieved the

17 criteria necessary to proceed to

18 transition.

19 And then a team were asked

20 to then establish, I think around that

21 time, I don't know if it was before,

22 during it or after it, a transition

23 strategy so as to enable what needed to

24 be done next to get to, more or less, the

1 next decision point and enter into the  
2 clinic and do the studies necessary.

3 Q. What --

4 A. I don't remember when a  
5 document was prepared, to whom it was  
6 presented, nor the -- an approval process  
7 that went along with that.

8 Q. Do you recall approximately  
9 when it was that that meeting took place,  
10 the DDC meeting?

11 A. I'm sorry, I don't.

12 Q. Was it before or after  
13 August of 2000?

14 A. I don't remember, I'm sorry.  
15 Likely -- I don't remember.

16 Q. As you sit here today, do  
17 you have a recollection as to whether  
18 this document, Exhibit 5, was prepared  
19 before or after the DDC meeting?

20 A. Either at it or after it.  
21 Not before it probably.

22 Q. I just point you to some --

23 A. But I don't remember  
24 exactly, I must say.

1 Q. I'd like to point you to  
2 subsections of this document for a  
3 moment.

4 A. Okay.

5 Q. And just ask you about it.  
6 If you turn to the second  
7 page of this document, under  
8 "Introduction and Background," the third  
9 paragraph down, it's the last two lines,  
10 states, "ABT-518" -- actually, watch me  
11 butcher this -- "ABT-518 possesses  
12 sub-nanomolar potency versus gelatinase  
13 B, an improvement of 200-fold over  
14 ABT-770."

15 First, did I butcher  
16 anything there?

17 A. No.

18 Q. Oh, good.

19 What does that mean?

20 A. It means it's a very, very  
21 potent molecule, so very little of it is  
22 needed to inhibit the enzyme, much less  
23 so than the predecessor compound. That's  
24 what sub-nanomolar is. That's

1     extraordinarily potent. And it's very  
2     selective. It says toward -- gelatinase  
3     B is one of the two enzymes we were most  
4     interested in, gelatinase A and  
5     gelatinase B.

6             So this is what that says.

7             Q. Is it fair to say that the  
8     more potent a compound is, the better  
9     that is in most circumstances, because  
10    you have to deliver less of the compound  
11    to the patient?

12            A. Generally.

13            Q. You -- you regarded it as a  
14    potential advantage of ABT-518, that it  
15    was more potent --

16            A. Yes.

17            Q. -- than ABT-770, correct?

18            A. Yes.

19            Q. The next sentence states,  
20    "ABT-518 is also a substantially more  
21    selective inhibitor of the gelatinases  
22    compared to prinomastat, suggesting that  
23    it may avoid mechanism-based joint  
24    effects."



1 Do you see that?

2 A. Yes.

3 Q. And that's a reference to  
4 the point I think that we made earlier  
5 today, which is that you thought that by  
6 selectively inhibiting these two specific  
7 enzymes, that ABT-518 might avoid some of  
8 the joint effects that were being seen  
9 with other MMPI compounds, is that right?

10 A. Yes.

11 Q. Again, you regarded that as  
12 a potential advantage for ABT-518,  
13 correct?

14 A. Yes.

15 Q. Now, the next line says, "In  
16 animal tumor models, ABT-518 demonstrated  
17 anti-tumor activity equal or superior to  
18 ABT-770 and prinomastat."

19 Do you see that?

20 A. Yes.

21 Q. Okay. At this point in  
22 time, did you think that ABT-518 was  
23 likely to be more efficacious than some  
24 of the other MMPI compounds that were

1 under development?

2 A. Yeah. Or at least as good

3 as, yeah.

4 Q. If you take a look at Page 4  
5 of this document, you see there's a chart  
6 there that says "MMP Inhibitors in  
7 Advanced Clinical Development."

8 Do you see that?

9 A. Yes.

10 Q. And one of them is  
11 marimastat, which we've discussed earlier  
12 today, correct?

13 A. Yes.

14 Q. And do you recall that was  
15 under development by British Biotech?

16 A. Yes.

17 Q. And then we also see  
18 prinomastat, which was under development  
19 by Agouron and Pfizer.

20 Do I have that correct?

21 A. Um-hmm.

22 Q. Near the bottom of that  
23 page, there's a reference to competition  
24 in the field for MMP inhibitors?

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1 A. Yes.

2 Q. It says that it was a  
3 compelling successor. What did that  
4 mean? In what way was it compelling?

5 A. Just that. Just the  
6 particular use of language in that  
7 document. I think you -- what you read,  
8 I think, summarized accurately the view  
9 that was held by most people, that with a  
10 highly selective inhibitor, that one  
11 could achieve efficacy. And, in part,  
12 the reason one could have reason to  
13 believe that one would achieve -- expect  
14 to achieve efficacy is that without the  
15 joint effects possibly caused by touching  
16 those other enzymes, you'd be able to  
17 continue to give this stuff so that it  
18 might be able to work.

19 So the selectivity being  
20 able to achieve -- enable the continued  
21 administration of the drug, where those  
22 others, you had to pause or stop because  
23 it had those untoward effects. So I  
24 think this summarized accurately the

1 view.

2 MR. LORENZINI: Could we  
3 take a break? Is there a problem  
4 with the microphone?

5 THE VIDEOGRAPHER: I've just  
6 got five minutes left on tape.

7 MR. DAVIS: Okay. That's  
8 fine. Thank you.

9 BY MR. DAVIS:

10 Q. Is it fair to say, Dr.  
11 Nisen, that you understood that one of  
12 the potential advantages of ABT-518 was  
13 that if it could avoid the joint effects,  
14 that patients who were taking 518 would  
15 be able to continue to receive the drug  
16 for longer periods of time and there  
17 hopefully -- therefore, hopefully benefit  
18 from the drug for longer periods of time  
19 than they would be if they took another  
20 MMPI?

21 A. That was an hypothesis.

22 Q. Was that hypothesis ever  
23 proven or disproven by Abbott?

24 A. It was never proven by

1 conducted anywhere other than in the  
2 Netherlands?

3 A. No.

4 Q. How did it come about that  
5 Abbott chose to do that study in the  
6 Netherlands?

7 A. We had good relationships  
8 with investigators there. We thought  
9 they did high quality studies and speed,  
10 they had a favorable regulatory and  
11 ethical review process. So we thought we  
12 could be more prompt, timely in our  
13 studies, conducting quality studies  
14 there.

15 Q. It says, "We will likely  
16 file a US-IND first quarter '01."

17 Did, in fact, Abbott file a  
18 US-IND for 518?

19 A. I don't remember.

20 Q. Were IND filings among the  
21 materials that you would expect Abbott to  
22 maintain in its regulatory files for 518?

23 A. Yes.

24 Q. And was -- had, to your

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1 don't recall specifically, and then I can  
2 follow up with a question about whether  
3 you have a general recollection. But  
4 what I'm trying to get at is whether you  
5 have any recollection, specific or  
6 general, when I ask these questions.

7 Do you understand that?

8 A. Yes, I do.

9 Q. Okay. And so my question I  
10 guess is, do you have any recollection,  
11 either specific or general, of  
12 criticizing or calling into question  
13 sales forecasts with respect to compounds  
14 in Abbott's oncology portfolio?

15 A. I remember thinking they  
16 were always a billion dollars no matter  
17 what. I'm being facetious. No. The  
18 answer is no.

19 MR. DAVIS: Let's mark this  
20 as the next exhibit.

21 (Exhibit No. Nisen-10,  
22 ABT-518 Descriptive Memorandum,  
23 February 2001, Bates  
24 ABBT0004032/0004039, was marked

1      for identification.)

2      BY MR. DAVIS:

3            Q.    This is Exhibit 10. Dr.

4      Nisen, I'm going to show you what's been

5      marked as Exhibit 10 at your deposition

6      and ask you if you've seen this document

7      before?

8            A.    Isn't this what you showed

9      me earlier?

10          Q.    Well, actually, I think,

11      sir, this is a different version of a

12      descriptive memo for ABT-518. I believe

13      that the document that you're referring

14      to is Exhibit 1, and that is a document

15      dated from May 31st, 2000.

16          A.    I see.

17          Q.    Or May of 2000 for the

18      meta -- matrix --

19          A.    Yes, I see that. I don't

20      remember the specific document.

21          Q.    Have you seen this document

22      before?

23          A.    I saw a document, and I

24      don't remember if it was this one or

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1 BY MR. DAVIS:

2 Q. And you can't give me any  
3 more information than you've already  
4 provided, correct?

5 A. No.

6 Q. What I said is correct?  
7 What I said is correct, you cannot give  
8 me any information beyond what you've  
9 already provided, is that right?

10 A. I don't -- I guess not.  
11 I've tried to answer your question as  
12 best I can.

13 Q. And I've tried to address  
14 your concerns the best I can. I don't  
15 know, within the confines of the English  
16 language, how I can make it any clearer.  
17 So I guess we'll have to move on and  
18 revisit that, if necessary, with the  
19 court.

20 All right. If you look on  
21 the bottom of Page 2 onto Page 3, the  
22 paragraph that begins, "ABT-518 displays  
23 no meaningful effects in genotoxicity."

24 Do you see that paragraph?



1 A. Yeah.

2 Q. Would you read that  
3 paragraph to yourself and tell me when  
4 you're done?

5 A. Okay.

6 Q. You see that there's a  
7 reference there to, again, to "ABT-518 is  
8 therefore a compelling development  
9 candidate with the potential to  
10 demonstrate anti-tumor effects superior  
11 to the MMP inhibitors currently  
12 undergoing clinical trials."

13 Do you see that?

14 A. Yeah.

15 Q. Do you -- did you believe  
16 that to be true as of February 2001?

17 A. Yeah.

18 Q. Did you believe it to be  
19 true as of March 2001?

20 A. I'm unable to distinguish  
21 for you what I believed in February  
22 versus March versus April versus May.

23 Q. At some point in time, did  
24 you come to believe that ABT-518 was not

1 shortcomings of the competitive products  
2 provide an opportunity for a compound  
3 with an approved SE or efficacy profile."

4 What is SE?

5 A. I'm not sure. Probably --

6 I'm -- probably safety profile, but I

7 don't know what SE stands for.

8 Q. It goes on to say, "Current  
9 animal models seem to predict Abbott's  
10 compound is superior to those currently  
11 in clinical trials, and has the potential  
12 to be best in class."

13 Do you believe that that was  
14 accurate as of February 2001?

15 A. Yes.

16 Q. And what does it mean to be  
17 best in class?

18 MR. LORENZINI: If you  
19 understand.

20 THE WITNESS: I think best  
21 means best.

22 BY MR. DAVIS:

23 Q. In what way?

24 A. I think any assessment of

1 any molecule is that clinical benefit  
2 ratio of benefit in the context of  
3 untoward effects, so that best ratio of  
4 working and untoward effects being better  
5 than the others.

6 Q. And did you believe at that  
7 point in time that if that was the case,  
8 that ABT-518 would have an advantage in  
9 the marketplace over other compounds,  
10 other MMPI compounds?

11 A. Yes.

12 Q. If you look at Page 6 of the  
13 document, under "Marketing overview,"  
14 there's a section titled "Side Effects."

15 A. That's what SE must refer  
16 to, then.

17 Q. SE refers to side effects?

18 A. Probably.

19 Q. If you read that paragraph  
20 to yourself and tell me when you're done,  
21 please.

22 A. Okay.

23 Q. The last sentence in that  
24 paragraph says, "As a critical Go/No Go

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1 And I take it that there  
2 were no final indications from any of  
3 those studies, because Abbott never  
4 conducted them, correct?

5 A. Correct.

6 MR. DAVIS: Okay. Stop here  
7 for lunch?

8 MR. LORENZINI: Sure.

9 THE VIDEOGRAPHER: Off tape,  
10 12:16.

11 (Luncheon recess is taken  
12 from 12:16 p.m. until 12:54 p.m.)

13 THE VIDEOGRAPHER: Stand by,  
14 please.

15 Back on the record, 12:54.

16 MR. DAVIS: Can you mark  
17 this, please, as the next exhibit?

18 (Exhibit No. Nisen-11,  
19 Abbott Portfolio Review, March  
20 7-9, 2001, Bates  
21 ABBT0013224/0013232, was marked  
22 for identification.)

23 BY MR. DAVIS:

24 Q. Dr. Nisen, you have what has

1 been marked as Exhibit 11 to your  
2 deposition, and I'm going to ask you if  
3 you've seen this document before?

4 A. Yesterday.

5 Q. Now, when is the last  
6 time -- had you seen it before yesterday?

7 A. Not that I really remember  
8 specifically.

9 Q. Do you have any general  
10 recollection of seeing this document  
11 before yesterday?

12 A. General recollection, yeah.

13 Q. Do you recall participating  
14 in an Abbott portfolio review on -- in or  
15 about early March 2001?

16 A. I can't remember the  
17 specific meetings that I participated in  
18 in 2000 --

19 Q. Do you have any recollection  
20 of those meetings?

21 A. Yes.

22 Q. Do you --

23 A. Of review meetings, yes.

24 Q. Okay. Do you have any

1 Q. But what did you -- you said  
2 there was a pause in enrollment.

3 A. For like a day or something.

4 Q. Do you recall what other  
5 effects there were, if any, as a result  
6 of the pause or the hold?

7 A. No. Other than having to  
8 call the investigator, I assume.

9 Q. Did you speak with any of  
10 the investigators about the pause or the  
11 hold on the 518 clinical trial?

12 A. No.

13 Q. Miss D'Amico goes on to  
14 state in her e-mail, "The next day we  
15 learned that the hold had been lifted."

16 A. Um-hmm.

17 Q. Again, I'll represent to you  
18 that Monday of this week was March 12th,  
19 2001, and that the next day would have  
20 been March 13th, 2001, and that was the  
21 day on which the John Hancock/Abbott  
22 research funding agreement was signed.

23 To your knowledge, was the  
24 decision within Abbott to lift the hold

1 on the Phase I clinical trial of ABT-518  
2 related in any way to the deal between  
3 John Hancock and Abbott?

4 A. Not to my knowledge.

5 Q. Who made the decision to  
6 lift the hold on the Phase I clinical  
7 trial of ABT-518?

8 A. I don't remember.

9 Q. Did you make that decision?

10 A. No.

11 Q. Did you have the authority  
12 at that time to make that decision?

13 A. I don't remember. Probably  
14 not.

15 Q. Do you recall learning at  
16 that point in time that someone had made  
17 a decision to lift the hold?

18 A. Not beyond reading what I  
19 read in the documents recently.

20 Q. So you have no independent  
21 recollection of the hold being lifted?

22 A. I think so. It's hard -- I  
23 can't separate from you independent  
24 recollection from having read this just

1 now, frankly.

2 Q. As best you can, Doctor, I'm  
3 going to ask you to tell me what you  
4 recall from your memory as opposed to  
5 what you've read in the documents  
6 concerning the lifting of the hold on the  
7 Phase I clinical trial of ABT-518.

8 What do you recall?

9 A. That we continued with  
10 development and enrolling subjects and  
11 carrying on as planned.

12 Q. Do you recall learning at  
13 some point in time, back in the 2001 time  
14 frame, that the hold had been lifted?

15 A. Very, very vaguely.

16 Q. Do you recall doing anything  
17 to determine why it was that the hold was  
18 lifted?

19 A. No.

20 Q. Did you ever learn, even if  
21 you don't recall right now, did you ever  
22 learn in that time frame why it was the  
23 hold had been lifted?

24 A. No.



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1 bottom e-mail from Mr. Deemer on or about  
2 March 20th, 2001?

3 A. No, I don't remember it.

4 Q. Do you recall writing the  
5 top e-mail to Mr. Deemer on or about  
6 March 21, 2001?

7 A. I don't recall the specific  
8 e-mail, but the points in there are of --  
9 are things I would have said. Some of  
10 them are personal.

11 Q. I'm not going to ask you  
12 about all of it. There are some pieces  
13 of these e-mails that I want to question  
14 you about.

15 A. Sure.

16 Q. First, Mr. Deemer wrote to  
17 you on March 20th, "You probably heard  
18 that Hancock was signed last week  
19 \$214,000,000 over 4 years! A long time  
20 coming but finally done. We had a little  
21 scare at the end when it looked like 518  
22 was being slowed down which could have  
23 been the deathnell to the deal. I worked  
24 with John to protest that and I

1 understand it is back on track."

2 Do you see that?

3 A. Yes, I see that.

4 Q. Do you recall having any  
5 discussions with Mr. Deemer about the  
6 subject matter in that e-mail?

7 A. No.

8 Q. When you received this  
9 e-mail from Mr. Deemer, do you recall  
10 understanding what he was referring to  
11 when he said it looked like 518 was being  
12 slowed down?

13 A. No. I don't recall.

14 Q. Do you have an understanding  
15 as to why slowing down 518 could have  
16 been the death knell to the deal between  
17 Abbott and John Hancock?

18 A. No.

19 Q. And then you -- did you have  
20 an understanding as to who John was that  
21 Mr. Deemer said he worked with to protest  
22 that?

23 A. I presume John Leonard.

24 Q. Did you ever have any

1 discussions with John Leonard about the  
2 subject matter of this e-mail?

3 A. Not that I remember.

4 Q. Did you understand what Mr.  
5 Deemer was referring to when he said that  
6 it -- it is back on track?

7 A. No. I mean, I assume it's  
8 back -- no more than what that says.

9 Q. Then you wrote in return, on  
10 the following day, "Phil, mega mazel tov!  
11 You are the most tenacious guy I know -  
12 you deserve a new car not just a pen. I  
13 know all about the 518 debacle (I tell  
14 you more over the phone)."

15 First, let me stop and ask,  
16 did you ever have that telephone  
17 discussion with Mr. Deemer?

18 A. I don't remember.

19 Q. And -- and what did you  
20 mean, Dr. Nisen, when you referred to the  
21 518 debacle? What was the 518 debacle?

22 A. I know. I don't remember.

23 Q. What do you regard as a  
24 debacle, what do you understand to be the

1 meaning of that term?

2 A. I tend toward hyperbole in

3 my e-mails, and you can see it from this

4 e-mail. So I think that's all that that

5 meant by that, which was kind of an

6 overstatement of some frustration.

7 Q. My question is slightly

8 different, which is, what do you

9 understand to be a debacle? How would

10 you define that term?

11 MR. LORENZINI: Objection.

12 Objection.

13 THE WITNESS: How do I

14 define its use in the English

15 language or what did I intend in

16 this e-mail?

17 BY MR. DAVIS:

18 Q. I'm going to first start

19 with your understanding of the meaning of

20 that term as it's used in the English

21 language.

22 A. It's --

23 MR. LORENZINI: Objection.

24 THE WITNESS: I think that's

1 germane.

2 Q. What data were presented at  
3 ASCO -- ASCO that caused -- you believe  
4 caused Abbott to terminate the  
5 development of ABT-518?

6 A. I don't remember the  
7 details. I do recollect that there were  
8 a series of negative studies across a  
9 series of molecules. I think around ten  
10 or so reports of negative kind of  
11 findings.

12 Q. Did they include negative  
13 results regarding marimastat?

14 A. I don't remember the  
15 details, but probably.

16 Q. And how about, is it  
17 prinomastat?

18 A. Again, probably, but I don't  
19 remember.

20 Q. Some of the information that  
21 you received, you heard at ASCO, was  
22 information that you knew about or had  
23 learned about prior to the ASCO  
24 conference, correct?

1 A. No.

2 MR. LORENZINI: Objection.

3 BY MR. DAVIS:

4 Q. None of the information that  
5 you heard at ASCO was information that  
6 you had learned before?

7 A. No. There's no information  
8 presented at the ASCO meeting that's  
9 presented -- if presented before the  
10 meeting wouldn't be eligible for  
11 presentation at that meeting.

12 Q. Well, you knew, for example,  
13 back in February of '01, that the  
14 development of marimastat had been  
15 terminated, correct?

16 MR. LORENZINI: Objection.

17 Asked and answered.

18 THE WITNESS: I actually,  
19 again, remember the details, but  
20 if there was a press release, I  
21 think you showed me one earlier  
22 today that said that. So what was  
23 publicly available was publicly  
24 available. I can't recall what

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1 the next exhibit.

2 (Exhibit No. Nisen-31, Memo,

3 8/10/01 on Abbott letterhead,

4 Bates ABBT0049970/0049977, was

5 marked for identification.)

6 THE WITNESS: Are you

7 accusing me of lying? Is that

8 what you're saying?

9 MR. LORENZINI: You don't

10 need -- you don't need to respond.

11 THE WITNESS: Well, let me

12 state on your record that I've not

13 been lying, that I don't lie and I

14 resent what I think was an

15 inference that I am.

16 MR. LORENZINI: I'm sure

17 it's unintended.

18 MR. DAVIS: I'm not going to

19 speak on your behalf, don't speak

20 on mine.

21 BY MR. DAVIS:

22 Q. Dr. Nisen, Exhibit 31 is in

23 front of you. Have you seen that

24 document before?

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1 A. I don't remember the  
2 specific document.

3 Q. Do you recall that after the  
4 decision was made within Abbott to  
5 terminate further development of ABT-518,  
6 you and some others within Abbott  
7 attempted to convince Abbott's management  
8 to resurrect the development of ABT-518?

9 A. I remember that Steve  
10 Davidsen, who was the discovery project  
11 leader, had strong views about trying to  
12 keep that alive. This is something that  
13 he worked on for almost a decade. And I  
14 remember that I thought we should  
15 follow -- finish up the study through, as  
16 stated in my other e-mails.

17 Q. And do you recall that you  
18 made recommendations to Abbott's  
19 management that they resurrect the  
20 development of ABT-518?

21 A. I don't remember resurrect,  
22 but in the e-mails that you showed me,  
23 its stated pretty clearly what my views  
24 were, I think, that I thought we should



1 finish that study.

2 Q. My question is a bit

3 different.

4 Do you recall after Abbott

5 decided to terminate the development of

6 ABT-518 in or about May or June of 2001,

7 that you and others within Abbott made an

8 effort to convince -- convince Abbott's

9 management to reverse that decision and

10 to reinstitute, to recommence the

11 development of ABT-518?

12 A. I don't remember

13 specifically.

14 Q. Do you recall receiving this

15 memo from Dr. Davidsen?

16 A. I think you asked me that

17 and I said I didn't remember exactly

18 receiving this document, but I do

19 recollect discussions with him, reasons

20 to believe and reasons to try to convince

21 others that we should continue trying to

22 develop the drug.

23 Q. If you take a look at the

24 page of this Exhibit 31 that's numbered

1 in the lower right-hand corner that ends  
2 in 49976, you see it says, under  
3 "Conclusion," it says, "To conclude, we  
4 feel that ABT-518 has the potential to be  
5 the first MMP inhibitor to demonstrate  
6 robust clinical efficacy. The points  
7 listed below provide a compelling  
8 argument as to why the development of  
9 ABT-518 should be continued."

10 Do you see that?

11 A. Yes.

12 Q. Did you agree with that  
13 statement at that point in time, as of  
14 August, 2001?

15 A. I don't remember what I  
16 specifically agreed to or generally  
17 agreed or disagreed with. These were the  
18 views that he expressed strongly and that  
19 he believed strongly.

20 Q. Did you pass his views along  
21 to Abbott's management?

22 A. I believe I did.

23 MR. DAVIS: Let's mark this  
24 as the next exhibit.

1 (Exhibit No. Nisen-32,  
2 Interoffice Memorandum, 8/14/01,  
3 Bates ABBT0049980/0049981, was  
4 marked for identification.)

5 THE WITNESS: Albeit in a  
6 more succinct way, I imagine.

7 BY MR. DAVIS:

8 Q. You have in front of you  
9 Exhibit 32. Have you seen this document  
10 before?

11 A. I saw it yesterday.

12 Q. Is this a memo, an  
13 interoffice memo that you sent to  
14 Mr. Norbeck and to Dr. Leonard?

15 A. Yeah.

16 Q. Is -- by the way, who is  
17 Mr. Norbeck?

18 A. That's -- Dr. Norbeck was --  
19 is the head of drug discovery at Abbott.

20 Q. When you sent this memo to  
21 Dr. Norbeck and to Dr. Leonard, were you  
22 hoping that they would recommence  
23 development of ABT-518?

24 A. I think I would have liked

1 to -- yeah, I think I would have liked to  
2 have seen us finish that study or find  
3 other ways to keep it alive.

4 Q. The very first line of the  
5 memo says, "Dan asked me to send"  
6 along -- I'm sorry.

7 "Dan asked me to send  
8 information that might convince him to  
9 revisit the decision regarding ABT-518  
10 development?"

11 Do you see that?

12 A. Yes.

13 Q. Did you want Dr. Norbeck to  
14 revisit the decision regarding the  
15 development of ABT-518?

16 A. I don't remember what my  
17 desires were specifically. But probably.

18 Q. Do you recall generally?

19 Did you believe that the  
20 arguments that Dr. Davidsen was making in  
21 his memo of August 10th were valid?

22 A. Yeah.

23 Q. And you believe they were  
24 valid even after you had seen the ASCO

1 data, right?

2 A. I think you're asking me

3 about two, two unrelated. So do one set

4 of results mitigate another set of

5 results? There are positive and negative

6 findings. So, are you asking me, on

7 balance, did I think then that, on

8 balance, it made more sense to continue

9 development and finish the study?

10 Q. Well, the ASCO conference

11 that you attended was in May of 2001,

12 correct?

13 A. Yeah.

14 Q. And even after the ASCO

15 conference, you agreed with Dr. Davidsen

16 that ABT-518 had the potential to be the

17 first MMPI inhibitor to demonstrate

18 robust clinical efficacy, correct?

19 A. That's what Steve Davidsen

20 wrote. And I believe that my view is I

21 would have liked to have seen that study

22 finish, and if there was a way to

23 continue its development, I would have

24 liked to have seen that.

1 Q. So you thought that even in  
2 the light of the ASCO data, that it made  
3 sense for Abbott to continue the  
4 development of ABT-518, correct?

5 MR. LORENZINI: At this  
6 time?

7 MR. DAVIS: At this time.

8 MR. LORENZINI: August 2001.

9 THE WITNESS: What I said  
10 there was, completion of that  
11 Phase I study would enable us to  
12 confirm that we can achieve  
13 exposure safely without events and  
14 that a small study could be  
15 performed to establish proof of  
16 principle. So I think that  
17 reflects what I believed at the  
18 time.

19 BY MR. DAVIS:

20 Q. Well, the very first  
21 sentence of your memo says, you're  
22 sending the information to Dr. Norbeck to  
23 try to convince him to revisit the  
24 decision regarding ABT-518 development.

1 And my question is, that you  
2 think more likely than not, you would  
3 have sought out the answer to that  
4 question back in the March 2001 time  
5 frame, correct?

6 A. I think so.

7 Q. Did you ever make any  
8 efforts to obtain funding for further  
9 development of ABT-518 outside of Abbott?

10 A. I think so, yeah.

11 Q. What did you do?

12 A. We had one meeting with a  
13 philanthroper, this guy Bill Goodwin,  
14 looking at alternative means for  
15 investment in assets, where he was  
16 looking to invest in cancer research in  
17 maybe some unique ways.

18 And I think we explored with  
19 him, Jeff and I, Leiden and I did explore  
20 with him whether he might fund  
21 translational experimental medicine  
22 research with Abbott molecules at  
23 academic institutions, and we might have  
24 included 518 in that mix.

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1 Q. When did you have those  
2 discussions with Mr. Goodwin?

3 A. I don't remember exactly  
4 when.

5 Q. It was after Abbott had  
6 decided to terminate development of  
7 ABT-518, is that right?

8 A. Probably, but I don't really  
9 remember when I met with him.

10 Q. Was it after you had  
11 attempted to get people within Abbott to  
12 revisit the decision to terminate the  
13 development of 518?

14 A. I don't remember.

15 Q. What was -- it's Mr.  
16 Goodwin?

17 A. (Witness nodding head.)

18 Q. What was Mr. Goodwin's  
19 response to your proposal?

20 A. He was not at all interested  
21 in the details of one molecule versus  
22 another, but the concept of how he might  
23 invest in cancer research in a unique  
24 way. And that was the focus of our



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1 Q. That's where you would go?

2 A. Yes.

3 Q. Who is Miss Lebold, by the  
4 way?

5 A. She was in business  
6 development. I don't know what her  
7 current position is.

8 Q. As you sit here today, do  
9 you recall any material transfer  
10 agreement having been signed with  
11 Vanderbilt concerning ABT-518 while you  
12 were employed at Abbott?

13 A. I don't know. Vaguely,  
14 maybe. I don't really remember. I don't  
15 remember.

16 Q. This e-mail leads you to  
17 believe that there was one, correct?

18 A. Yeah, seems like it.

19 MR. DAVIS: Let's mark this  
20 as the next exhibit.

21 (Exhibit No. Nisen-37,  
22 E-mail string, 9/23/02, Bates  
23 ABBT334838/334841, was marked for  
24 identification.)

1 BY MR. DAVIS:

2 Q. Dr. Nisen, you have in front  
3 of you Exhibit 37, which are some  
4 e-mails, and attached to the e-mails is a  
5 project overview for ABT-518.

6 Have you seen these  
7 documents before?

8 A. No, not that I remember.

9 Q. Did you participate in any  
10 out-licensing activities regarding  
11 ABT-518?

12 A. I was probably asked for  
13 information and helped provide a package  
14 and a dossier, and if I knew anybody that  
15 might be interested.

16 Q. You recall doing that?

17 A. Only in the vaguest way.  
18 But I think I did.

19 Q. When you worked at Abbott,  
20 did you ever participate in any  
21 in-licensing activities?

22 A. Yes.

23 Q. How many occasions?

24 A. I struck some -- a couple

1 THE VIDEOGRAPHER: We're  
2 back on the record. This is the  
3 beginning of Tape 4. The time is  
4 4:11.

5 BY MR. DAVIS:

6 Q. Dr. Nisen, did Abbott  
7 out-license ABT-518 while you were  
8 employed at Abbott?

9 A. No.

10 Q. Why not?

11 A. I think it's very hard to  
12 out-license drugs.

13 Q. What efforts, if any, do you  
14 know of that Abbott made to out-license  
15 ABT-518?

16 A. I think they shopped it to a  
17 lot of different companies, actually.

18 Q. How do you know that?

19 A. I just remember vague  
20 discussions of them going around and  
21 trying.

22 Q. Who did it? Who made those  
23 efforts?

24 A. I don't remember who was in

1 charge of business development then.

2 Q. Who did they talk to?

3 A. You're going to have to ask  
4 them who they spoke to.

5 Q. And what responses did they  
6 receive?

7 A. Again, you're going to have  
8 to ask them, but I think, in general,  
9 it's been -- I think that field has  
10 really been shut down as an area of  
11 investigation, and I think there's just  
12 no enthusiasm in the medical/scientific  
13 community for MMPs as a therapeutic  
14 intervention in cancer anymore.

15 Q. That's your understanding?

16 A. Yes.

17 Q. Are you still -- do you  
18 still follow that field?

19 A. No. Not closely.

20 Q. Did you have any -- do you  
21 know anything more about Abbott's  
22 out-licensing efforts with respect to  
23 ABT-518, other than what you've now told  
24 me?

1 some questions, but we need to  
2 pause for a minute. Can we take a  
3 break?

4 THE VIDEOGRAPHER: Off tape,  
5 4:13.

6 (Recess is taken from  
7 4:13 p.m. until 4:18 p.m.)

8 THE VIDEOGRAPHER: Stand by.  
9 Back on the record, 4:18.

10 - - -

11 EXAMINATION

12 - - -

13 BY MR. LORENZINI:

14 Q. Dr. Nisen, could you turn to  
15 Exhibit 10, please.

16 A. Got it.

17 Q. This is the descriptive  
18 memorandum dated February 2001 for  
19 ABT-518 that you reviewed previously.

20 A. Yeah.

21 Q. Did you have an opportunity  
22 to review this document in preparation  
23 for your deposition?

24 A. A little bit yesterday and

1 read through it again today.

2 Q. So you're familiar with

3 the -- the contents?

4 A. Yes.

5 Q. Based on everything you know

6 today, do you believe Exhibit 10 to be a

7 complete and accurate summary of the

8 status and prospects of ABT-518 as of

9 March 2001?

10 A. Yes.

11 MR. DAVIS: Objection.

12 You can respond.

13 THE WITNESS: Yes.

14 MR. LORENZINI: I'd like to

15 mark as a new exhibit number --

16 THE WITNESS: Maybe I'll

17 just add, there are a mountain --

18 there is a mountain of information

19 about MMPIs, positive and

20 negative. In aggregate taken

21 together, I do believe this is an

22 accurate representation of the

23 molecule and the state of affairs

24 in the field at the time. To be

1 comprehensive, would have been a  
2 telephone book or more.

3 BY MR. LORENZINI:

4 Q. But you believe this to be a  
5 comprehensive summary --

6 A. Accurate --

7 Q. -- of the -- the relevant  
8 information?

9 A. I really do, yes.

10 (Exhibit No. Nisen-38,  
11 E-mail, 5/22/01, Bates  
12 ABBT0064226, was marked for  
13 identification.)

14 MR. LORENZINI: Why don't we  
15 just -- let me take that back for  
16 a second. I'll just show it to  
17 you, Brian, for a second.

18 MR. DAVIS: Thank you.

19 BY MR. LORENZINI:

20 Q. Dr. Nisen, you have before  
21 you what the court reporter has marked as  
22 Exhibit 38. Could you just take a moment  
23 to review this document, please?

24 A. Okay.

1 Q. I'll just state for the  
2 record this appears to be a May 22nd,  
3 2001 e-mail from Perry Nisen to John  
4 Leonard with an attached document  
5 entitled ASCO 2001 MMPI update.

6 A. Right.

7 Q. Dr. Nisen, do you recognize  
8 this document, the e-mail and the  
9 attachment?

10 A. Vaguely now.

11 Q. Do you think this is an  
12 e-mail and attachment that you sent to  
13 John Leonard?

14 A. Yeah. I mean, it says it  
15 was from me. I have no reason to think I  
16 did not. No specific recollection of the  
17 document, but...

18 Q. Did you attend the ASCO  
19 conference in 2001?

20 A. You know, I can't remember  
21 if I was there myself or not. Probably.

22 Q. Whether you were there  
23 personally or not, do you remember  
24 getting results regarding competitors'



1 drugs at the 2001 ASCO conference?

2 A. Yeah, from -- from the

3 conference.

4 Q. And does the attachment

5 that's part of Exhibit 38 provide a

6 summary of what you recall basically

7 being the presentations from the ASCO

8 conference?

9 A. I have no reason to believe

10 they're not accurate.

11 Q. And you testified earlier

12 that you recalled some negative

13 information regarding competitor MMPI

14 compounds being released at the 2001 ASCO

15 conference in May --

16 A. Yes.

17 Q. -- of 2001.

18 Does this attachment that's

19 part of Exhibit 38 provide a fair summary

20 of the negative information that you

21 recalled receiving from the ASCO

22 conference?

23 A. Yes.

24 Q. And what -- what was it

1 about the findings that were presented at  
2 the May 2001 ASCO conference that you  
3 believe to be negative?

4 A. I think the totality of the  
5 negative findings, so ten abstracts, all  
6 basically negative as to efficacy and  
7 some increasing evidence of toxicity.  
8 But most important, I think, was just  
9 added to the body of negative evidence  
10 for lack of efficacy.

11 Q. And were these ten abstracts  
12 presented for the first time at the ASCO  
13 conference in May, to your knowledge?

14 A. Yes.

15 Q. These abstracts weren't  
16 something you reviewed prior to the  
17 conference?

18 A. Could not have. So by  
19 definition, to be accepted for  
20 presentation at ASCO is predicated upon  
21 the agreement that they -- those data  
22 will not have been -- would not have been  
23 presented elsewhere prior. They're  
24 pretty careful about that.

1 Q. And so the information from  
2 the ten abstracts that's summarized in  
3 this presentation was new information  
4 that was not available to Abbott prior to  
5 the ASCO conference in May 2001?

6 A. Correct.

7 MR. DAVIS: Objection.

8 THE WITNESS: Correct.

9 BY MR. LORENZINI:

10 Q. And you testified earlier  
11 that the decision to terminate ABT-518 in  
12 either late May or early June was related  
13 in some way to the new information that  
14 was made available at the ASCO conference  
15 in May, is that correct?

16 A. I think influenced by it.  
17 And that was, I think, part of the aegis  
18 to communicate these data. I think  
19 everyone was anxious to see what the new  
20 data and findings were, recognizing that  
21 there were a lot of clinical studies  
22 underway with competitor molecules.

23 Q. So the information contained  
24 in Exhibit 38 from the ten abstracts,

1 that was not available in -- not  
2 available to Abbott in March 2001?

3 MR. DAVIS: Objection.

4 THE WITNESS: I don't think  
5 they were available to anybody.

6 MR. LORENZINI: I'd like to  
7 mark a new exhibit.

8 (Exhibit No. Nisen-39,  
9 E-mail string, 5/28/01, Bates  
10 ABBT0033486/0033494, was marked  
11 for identification.)

12 BY MR. LORENZINI:

13 Q. Dr. Nisen, you have before  
14 you what's been marked as Exhibit 39.  
15 It's an e-mail from Diane Bronson to  
16 Diane D'Amico dated May 28th, 2001, with  
17 an attached document entitled "ASCO 2001  
18 MMPI Update."

19 A. Okay. Looks like the same  
20 thing that we just looked at.

21 Q. Right.

22 A. The attachment is.

23 Q. Do you recall that we looked  
24 at an e-mail chain before that Mr. Davis

1 showed you that was similar to the e-mail  
2 chain -- that included the e-mail chain  
3 that's now been marked as Exhibit 39?

4 A. Yeah.

5 Q. And -- maybe we should turn  
6 back to that.

7 A. And I remember that it was a  
8 partial -- it was two or three of those  
9 slides, but not the complete slide deck.

10 Q. The earlier exhibit that Mr.  
11 Davis showed you?

12 A. Yeah, I remember that.

13 Q. And does this appear to be  
14 the complete attachment to the e-mail  
15 that you received?

16 A. Yes.

17 MR. DAVIS: Objection.

18 You're asking if he recalls  
19 whether this is the complete  
20 attachment or you're just asking  
21 whether he can, looking at it now,  
22 he's making that judgment?

23 BY MR. LORENZINI:

24 Q. Well, first I'll ask, do you

1 recall this attached multi-page

2 presentation?

3 A. No, not really.

4 Q. But you recall generally a

5 presentation being prepared regarding the

6 ASCO findings?

7 A. Vaguely, given my e-mail.

8 Q. All right. And you -- on

9 Exhibit 39, there's an e-mail, May 22nd,

10 2001, from you to Azmi Nabulsi attaching

11 ABT-518 slides.

12 Based on your review of this

13 e-mail and the attachment that's been

14 marked as Exhibit 39, do you believe this

15 to be a complete set of the attachments?

16 MR. DAVIS: Objection.

17 THE WITNESS: Seems --

18 MR. DAVIS: You can respond.

19 THE WITNESS: Seems like it.

20 BY MR. LORENZINI:

21 Q. If you'll turn to the last

22 page of Exhibit 39, there's ABT-518

23 development recommendations.

24 Do you recall recommending

1 continuation of the Phase I clinical  
2 trial in late May?

3 A. I think so. I think this  
4 probably does reflect my consistent  
5 personal view that we should see the  
6 study through, that we should complete  
7 the Phase I study, that we should get a  
8 target dose, stop it if there was  
9 toxicity, stop if there was -- basically  
10 stop for toxicity and that there was a  
11 small proof of concept, proof of  
12 principle study that we could still do.  
13 I still --

14 Q. Why did you believe at that  
15 time that -- strike that.

16 Why were you recommending  
17 that approach in late May of 2001?

18 A. It's hard to remember  
19 exactly where I was and what I felt at  
20 the time, but, again, it just seemed like  
21 my responsibility. And I felt as the  
22 advocate for this asset, that -- to  
23 always look for a path forward to see if  
24 there was something there, to still look

1 for a way forward.

2 Q. So the ASCO findings were

3 negative, but you believed there was

4 potentially some ability of ABT-518 to

5 distinguish itself from the competitor

6 compounds?

7 MR. DAVIS: Objection.

8 You can respond.

9 THE WITNESS: I think,

10 again, in the absence of efficacy,

11 I think what this reflects is a

12 statement of maybe there's still a

13 path forward to be able to

14 demonstrate some signal of

15 activity, even in the face of

16 those fairly large negative other

17 studies. At one point, one says

18 enough already is hard to say. In

19 the retrospect, it's easy, I think

20 at that moment of time.

21 BY MR. LORENZINI:

22 Q. And management at Abbott

23 terminated ABT-518 development soon after

24 the ASCO studies were released?



1 A. I think so. I think that

2 was the timing.

3 (Exhibit No. Nisen-40,

4 E-mail string, 6/11/01, Bates

5 ABBT0063625, was marked for

6 identification.)

7 BY MR. LORENZINI:

8 Q. Dr. Nisen, you have before

9 you what's been marked as Nisen

10 Exhibit 40. It's an e-mail chain

11 beginning with a June 11th, 2001 e-mail

12 from you to Steven Davidsen.

13 Do you recognize this e-mail

14 chain? Is this an e-mail that you wrote

15 in June 2001?

16 A. Looks like it, yeah.

17 Q. And do you recall receiving

18 some data from Steven Davidsen regarding

19 the -- the clinical trials of ABT-518?

20 A. Yeah, vaguely, in that they

21 were good exposures.

22 Q. What do you mean by "good

23 exposures"?

24 A. Good exposure meaning you

1 can measure it in the blood and it lasted  
2 there from even those few subjects  
3 treated.

4 Q. What is the benefit of that?

5 A. As opposed to not having  
6 exposures, so that it was -- you took it,  
7 it got absorbed, it was there in the  
8 blood, it stayed in the blood. And that,  
9 to the question that was asked of me  
10 earlier with respect to metabolites, this  
11 measures a bunch of the metabolites. And  
12 one sees, in fact, that the parent drug  
13 exposures are higher and that there is --  
14 don't seem to be gigantic amounts of  
15 metabolites over time and accumulate --  
16 or accumulating, and actually much less  
17 than the parent drug.

18 So while there were  
19 statements and concerns regarding  
20 metabolites, and the question was asked,  
21 was there evidence that it wasn't allowed  
22 to be seen through to answer that. There  
23 are pretty good data here that you can  
24 measure those metabolites, many of them.

1 And they look pretty level, much lower  
2 than the parent drug. It's a log -- a  
3 log scale rendition of those data, so --

4 Q. If you look at  
5 Mr. Davidsen's June 11th e-mail to you,  
6 the second one down, he states, "Perry,  
7 this data ain't bad...damn near target  
8 exposure with 25 milligram dose.  
9 Metabolites are low at 22 days, no  
10 apparent induction of metabolism.  
11 Independent of whether ABT-518 is pursued  
12 further, I think it's safe to say that  
13 the decision to take it into clinical  
14 studies was not stupid..."

15 Was it -- maybe I'll read  
16 also your response. In response, you  
17 say, "Damn right."

18 Was it your belief at this  
19 time, as of June 11th, 2001, that  
20 Abbott's decision to take ABT-518 into  
21 Phase I clinical development was a smart  
22 decision?

23 A. Yes.

24 Q. And that's because you

1 believed at the time that it was taken  
2 into Phase I clinical trials that it had  
3 promise?

4 A. For the right reason, and I  
5 had said earlier that it seemed like --  
6 and in that document, that summary, I  
7 referred to favorable pharmaceutical  
8 properties. And I think these data  
9 affirm that, that it had really good  
10 pharmaceutical properties, that it got  
11 into the blood. And even at the doses,  
12 the first doses we gave, achieving  
13 exposure in the blood, quite near what we  
14 thought you needed to have, is what we  
15 targeted to have, which is very  
16 encouraging. And that its half-life was  
17 good, so it stayed there. And that there  
18 weren't those metabolites that were of  
19 concern from the preclinical data.

20 So this provided human  
21 clinical evidence that you --  
22 approximately, what a proper dose was,  
23 that it would achieve those exposures,  
24 that there wasn't metabolism -- that

1 there was some metabolism, but not the  
2 untoward kinds of metabolism that people  
3 were concerned about.

4 So it actually already  
5 answered a lot of questions that could be  
6 answered from that kind of a Phase I  
7 study. Perhaps luckily it did.

8 MR. LORENZINI: I have no  
9 further questions.

10 MR. DAVIS: Okay.

11 - - -

12 FURTHER EXAMINATION

13 - - -

14 BY MR. DAVIS:

15 Q. Dr. Nisen, I want to make  
16 sure I have your testimony correct.

17 You've now reviewed  
18 Exhibit 10, which is the February 2001  
19 descriptive memo for ABT-518.

20 A. Yes.

21 Q. And it's your testimony, if  
22 I have it correct, that this is a  
23 comprehensive and accurate description of  
24 the status of that compound as of March

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## **Deposition Exhibit No. 2**

**D's Exhibit 825**

**ABT-518**

1 of 1

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February 2001

ABT-518

## Monthly Highlights – Key Project Progress

- Study initiation visits were conducted on 2/14 and 2/15.

| Key Progress  | Next Quarter's Key Project Milestones | Target Date |
|---|---------------------------------------|-------------|
| • First patient enrolled                                      |                                       | 3/12        |
| • Preliminary results from 6-week rat hepatotoxicity study    |                                       | 3/31        |
| • Pre-IND meeting with FDA                                    |                                       | 6/1         |
| • Preliminary results from 3-month rat chronic toxicity study |                                       | 6/30        |

| Risk of Failure  | Potential Unknown Impact   | Phase I IND study to Transition program to solicit FDA input.  | Resolution Date            |
|--|--|--|----------------------------|
| Identification of FDA requirements for cytotoxic agents in oncology drug development.  | <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory<br>Chemical synthesis, process, and formulation | Phase I IND study to Transition program to solicit FDA input.  | Planned / Actual<br>6/1/01 |
| Key tox finding was hepatotoxicity in one-month rat study. <i>In-vitro</i> and <i>in-vivo</i> data indicate a potential for mechanism based drug interactions. | <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input checked="" type="checkbox"/> Regulatory<br>Chemical synthesis, process, and formulation | The Phase I first-in-man protocol has been designed to address these issues. A 6-week tox and metabolism studies have been completed. Results are under review. A 3-month rat toxicity study is ongoing. | 7/1/01                     |

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| Risk of Issue   | Potential Known Impacts<br><small>Check all that apply and describe impact</small>   | Strategy for Mitigation  | Competitive Environment | Resolution Date<br><small>Planned / Actual</small> |
|---|--|--|-------------------------|--|
| As several competitors are in Phase I/II, ABT-518 product profile will need to demonstrate advantage over the other compounds (i.e., safety/efficacy) | <input type="checkbox"/> Cost <input type="checkbox"/> Time <input checked="" type="checkbox"/> Profile <input type="checkbox"/> Regulatory<br><input type="checkbox"/> All that apply and describe impact | Ongoing analysis and comparison of competition throughout transition. ABT-518 has the potential to be the best in class compound. Pfizer (Agouron) announced 8/4/00 that they were stopping Phase III trials of pinomastat in advanced prostate and NSCLC because "primary efficacy objectives were not met". They are continuing trials in less advanced tumors, e.g., glioma and NSCLC, and will start trials in two additional tumor types. Efficacy was shown with marimastat in less advanced gastric cancer, but British Biotech announced on 9/27/00 that marimastat in combination with carboplatin was no better than carboplatin alone in advanced ovarian cancer. <b>Marimastat development was discontinued on 2/15/01.</b> Both the Pfizer compound and British Biotech's compound are hindered by dose-limiting joint toxicity | Competitive Environment |  |
|   | <input type="checkbox"/> Cost <input type="checkbox"/> Time <input type="checkbox"/> Profile <input type="checkbox"/> Regulatory   |  |                         |  |

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February 2001

ABT-518

## Key Activities

| Commercial   |  | LBE       | Actual |
|--|--|-----------|--------|
| Activity   |  |           |        |
| Market research to assess commercial potential of cancer types, both US and Ex-US... |  | 4/2001    |        |
| Assessment of patient compliance (for revision of forecast)                          |  | 3/2001    |        |
| Assessment of off label vs. spillover use (for revision of forecasts)                |  | 3/2001    |        |
| Assessment of cancer market growth (for revision of forecasts)                       |  | 4/2001    |        |
| Assist with advisory planning  |  | 4/2001    |        |
| Development of brand and generic names   |  | Late 2001 |        |

| Formulation                              |  | Plan    | Actual |
|--|--|---------|--------|
| Activity                                 |  |         |        |
| Phase I Formulation                      |  | 10/2000 |        |
| Phase II Formulation                     |  |         |        |
| Formulation for Bio Study                |  |         |        |
| Phase III Clinical Supplies Manufactured |  |         |        |
| NDA Lots (3) Completed                   |  |         |        |
| Completion of 1 Year Stability for NDA   |  |         |        |
| Formulation Peer Review                  |  |         |        |

| Drug Substance   |         | Plan   | Actual  | Actual Projected Cost/kg |
|------------------|---------|--------|---------|--------------------------|
| Activity         | KG      |        |         |                          |
| Chem Scien (GLP) | 3.0/1.7 | 6/2000 | 6/1900  | \$133,300                |
| Chem Scien (GMP) | 2.0/0.9 | 6/2000 | 6/29/00 | \$133,300                |
| Chem Scien       | 15.0    | 6/2001 |         |                          |
| SPD              |         |        |         |                          |
| SPD              |         |        |         |                          |
| SPD              |         |        |         |                          |
| Demo Lot         |         |        |         |                          |
| NDA Lot #1       |         |        |         |                          |
| NDA Lot #2       |         |        |         |                          |
| NDA Lot #3       |         |        |         |                          |
| Validation Lot   |         |        |         |                          |

| Toxicology                           |  | Planned Start | Actual Start Date | Report Completed |
|--------------------------------------|--|---------------|-------------------|------------------|
| Toxicology Activity                  |  |               |                   |                  |
| Gene Toxicology                      |  | 5/2000        |                   |                  |
| Acute Studies                        |  | 5/2000        |                   |                  |
| 2-Week Monkey (non-GLP)              |  | 12/1999       | 12/14/99          |                  |
| 1-Month Rat (non-GLP screening)      |  | 12/1999       | 12/14/99          |                  |
| 1-Month Rat (GLP)                    |  | 6/2000        | 6/27/00           |                  |
| 1-Month Monkey (GLP)                 |  | 6/2000        | 6/29/00           |                  |
| 3-Month Rat                          |  | 1/2001        | 1/2/01            |                  |
| 3-Month Mouse MTD                    |  |               |                   |                  |
| SEG I and SEG II                     |  |               |                   |                  |
| SEG III Rat (post netai development) |  |               |                   |                  |
| 6-Month Rat                          |  |               |                   |                  |
| 1-Year Monkey                        |  |               |                   |                  |
| Carcinogenicity (2 yr) Rat           |  |               |                   |                  |
| Carcinogenicity (2 yr) Mouse         |  |               |                   |                  |

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ABT-518

**All Clinical Studies:**

| Protocol Number | Phase | Study Name                  | Protocol Number | Phase | Study Name | Start 1 <sup>st</sup> Pt. Dosed | End (Last CRF In) | Patients |         |
|-----------------|-------|-----------------------------|-----------------|-------|------------|---------------------------------|-------------------|----------|---------|
|                 |       |                             |                 |       |            |                                 |                   | Target   | Current |
| M00-235         | I     | MD Study in cancer patients |                 |       |            | 2/28                            |                   | 40       |         |
| TB0             | I     | IND Study                   |                 |       |            |                                 |                   | 20       |         |

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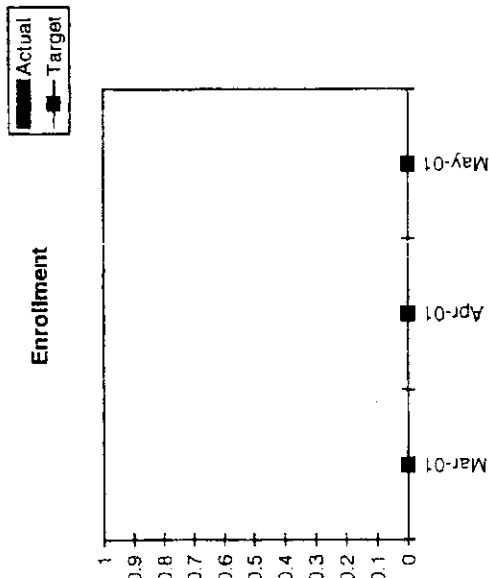
February 2001

ABT-518

# Ongoing Clinical Studies (List first time in man, Phase II Dose-Ranging and Pivotal Trials)

Protocol: M00-235 - Phase I MD in cancer patients  
 Objective: Determine MTD and safety profile in cancer patients  
 ABT-518 Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day  
 Comparator Doses: N/A  
 Target Enrollment: 40  
 Status: Study initiated, clinical supplies delivered  
 Major Findings:

XXX-XXX - TITLE



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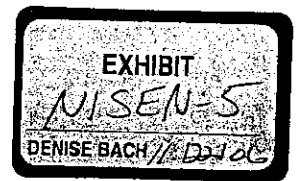
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5

## **Deposition Exhibit No. 5**

**D's Exhibit 826**



**ABT-518**

**TRANSITION STRATEGY**

**(MMPI)**

**August 2000**

Confidential

ABBT256634



*ABT-518 Transition Strategy*  
August 2000

## ABT-518 TRANSITION STRATEGY

### 1. Introduction and Background

For most cancers, the level of physician satisfaction with current therapies is low given the highly toxic nature of the treatments. A new avenue being investigated is the use of "cytostatic" agents. This approach to therapy has the potential to transform cancer into a chronic disease that patients live with long-term, much like the effect protease inhibitor therapy has had on patients with HIV infection. Abbott's matrix metalloproteinase inhibitor (MMPI) program is one example of this novel therapy with the potential to alter the way cancer is treated by preventing or modifying disease progression and/or metastases.

The MMPs comprise a family of enzymes that degrade a wide range of tissue matrix protein substrates. Many solid tumors have high expression of these enzymes and this is associated with the ability of tumors to aggressively grow, invade, develop new blood vessels and metastasize. Experimental evidence suggests that the MMPs gelatinase A and gelatinase B are particularly important in tumor progression. The Discovery Project Team has therefore targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes severe joint pain and stiffness that precludes the use of high doses in clinical trials. The joint-related adverse events are believed to be related to the inhibition of other MMPs, namely MMP-1 (fibroblast collagenase).

ABT-518, a member of Abbott's biaryl ether retrohydroxamate series of inhibitors, replaced ABT-770 as the lead MMPI transition candidate. Preclinical toxicity studies with ABT-770, Abbott's first MMP inhibitor development candidate, revealed a number of adverse effects which occurred at drug exposures only several fold higher than that necessary for efficacy in animal models. The MMP selectivity and potency profile exhibited by ABT-518 distinguish it from ABT-770 and the competitor's compounds. ABT-518 possesses sub-nanomolar potency versus gelatinase B, an improvement of 200-fold over ABT-770. ABT-518 is also a substantially more selective inhibitor of the gelatinases compared to prinomastat, suggesting that it may avoid mechanism-based joint effects.

In animal tumor models, ABT-518 demonstrated anti-tumor activity equal or superior to ABT-770 and prinomastat. Inhibition of tumor growth was dose dependent in both syngeneic and xenograft models. Infusion studies with osmotic minipumps designed to determine the minimal blood levels necessary for efficacy showed that steady-state blood levels of ABT-518 ranging from 0.13 µg/ml (B-16 syngeneic melanoma) to 0.57 µg/ml (HT1080 human fibrosarcoma) resulted in biologically significant inhibition (defined as ≥ 30% inhibition of tumor growth over that of control). Comparable efficacy via the oral route was achieved with doses, given twice a day, of 3 and 10 mg/kg, respectively, in the two experimental models. These doses would be roughly 200-800 mg in humans. ABT-518 was also effective in blocking blood vessel formation in a mouse ocular model of angiogenesis.

ABT-518 gave sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailability ranged between 68 and 93% depending on formulation and species. Multiple metabolites are produced after repeated oral dosing, some reaching plasma concentrations in excess of

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parent drug. Most of the metabolites result from modification of the retrohydroxamate moiety, although the relative amounts vary with gender and species. Plasma concentrations will be assessed in Phase I to determine safety margins and potential drug-drug interactions.

The preclinical safety profile exhibited by ABT-518 is more favorable than ABT-770. ABT-518 displays no significant effects in screening studies for genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. Toxicity studies in rats and monkeys (non-GLP) reveal none of the debilitation and lethality seen with ABT-770. Tissues from these animals reveal no evidence of phospholipidosis which likely reflects the reduced tissue burden of metabolites produced by ABT-518 relative to ABT-770. Plasma concentrations generated by ABT-518 in rat toxicity studies are at least 20-fold higher than that necessary to produce efficacy in animal tumor models.

Several orally bioavailable MMP inhibitors are being assessed in phase II/III clinical trials for the treatment of cancer (Table 1). Preliminary results from several trials suggest that treatment with an MMPi can cause disease stabilization. Results from Phase III studies with marimastat have been both positive (gastric cancer) and negative (pancreatic cancer and glioma) and suggest that MMP inhibitors are more likely to benefit patients at earlier stages of disease progression. A survival benefit for marimastat was seen in 101 inoperable gastric cancer patients without metastases ( $p=0.033$ ). However, all but tanomastat report dose-limiting side-effects characterized by pain and stiffness of the joints (BMS-275291 showed Grade 1/2 joint effects). Although tanomastat is highly gelatinase selective, it exhibits only marginal to modest potency against MMP-2. The incidence of joint toxicity exhibited by marimastat, prinomastat, and BMS-275291 may negatively influence the likelihood of their ability to demonstrate efficacy in Phase II/III studies. Doses of 5, 10 and 25 mg administered BID were chosen for the Phase III trials for marimastat. These are below the dose at which joint toxicity was observed in Phase I. Seven other randomized pivotal trials with marimastat are currently ongoing in SCLC, NSCLC, breast cancer, ovarian cancer, and in glioblastoma. Pfizer announced on 8/4/00 that Phase III clinical trials of prinomastat in patients with advanced non-small cell lung cancer (NSCLC) (in combination with paclitaxel/carboplatin and with gemcitabine/cisplatin) and in advanced hormone-refractory prostate cancer patients (in combination with mitoxantrone/prednisone) have been discontinued. The reason given was that "primary efficacy objectives were not met". Both studies assessed the effect of prinomastat at doses of 5, 10, and 15 mg BID. These dose levels are below the doses at which joint pain was observed in Phase I. They are continuing trials in less advanced tumors, e.g., esophagus, melanoma, breast, glioma, and NSCLC and will start trials in two additional tumor types.

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**Table 1. MMP Inhibitors in Advanced Clinical Development**

| MMP Inhibitor<br>Company                   | Development<br>Stage | Tumor<br>Type  | Metalloproteinase<br>Selectivity   | Joint<br>Toxicity |
|--|----------------------|--|------------------------------------|-------------------|
| Marimastat<br>British Biotech/<br>Schering | Phase III            | NSCLC<br>SCLC<br>breast<br>ovarian                               | Broad spectrum                     | yes               |
| Prinomastat<br>Agouron/<br>Pfizer          | Phase III            | esophagus<br>melanoma<br>breast<br>glioma<br>NSCLC*<br>Prostate* | Moderately gelatinase<br>selective | yes               |
| BMS-275291<br>BMS/Chirosciences            | Phase I/II           | unknown  | Broad spectrum; no<br>TACE         | yes               |
| Tanomastat†<br>Bayer                       | Phase III            | SCLC<br>NSCLC<br>ovarian<br>pancreatic                           | Highly gelatinase<br>selective     | No                |
| ABT-518<br>Abbott Labs                     | Precinical           |  | Highly gelatinase<br>Selective     | TBD               |

\* Discontinued in advanced disease. NSCLC continues in less advanced disease.

† Tanomastat (BAY12-9566) was discontinued from clinical development when an interim analysis of a study revealed increased mortality in the drug treated group. However, subsequent analysis of additional patients showed drug benefit and Bayer may resume clinical development (personal communication).

While the competition in the MMP inhibitor field is intense, no compound has yet been approved. The selectivity of ABT-518 suggests that it may be spared the dose-limiting joint toxicity observed with marimastat and prinomastat, thus expanding the range of tolerated doses and enhancing the likelihood of demonstrating clinical efficacy. ABT-518 is therefore a compelling successor to ABT-770 with the potential to demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials.

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## 2. Transition Strategy

### 2.1. Objectives/attributes

The primary objective of the transition process will be to assess key attributes of ABT-518 that would justify a recommendation for full development or program discontinuation. Key desirable attributes for ABT-518 include:

- Acceptable animal toxicity profile following prolonged administration (one-month in two species).
- Favorable systemic exposure (0.1 µg/ml trough concentration) in cancer patients after oral administration not more than twice a day.
- Acceptable safety profile in cancer patients following a minimum treatment of one month.

The development activities during the transition period will be limited to two Phase I studies (a first-in-man multiple-escalating dose study ex-US and a small IND study), and the toxicology, metabolism and formulation activities needed to support Phase I activities. It is not the objective of the transition program to demonstrate proof of efficacy for this compound, as this can only be assessed during properly controlled studies.

Several Go/No Go decision points have been incorporated into the transition program, which has an overall objective of making a timely recommendation for the continuation of ABT-518 development or program discontinuation. The key Go/No-Go points are related to (1) preclinical toxicity (Sep 2000), and (2) safety and pharmacokinetics in patients from the multiple-dose study (Dec 2001). Throughout the transition, attention will be paid to the competitive environment by tracking the progress of other MMPIs in development.

### 2.2. Key Issues/Risk Assessment

While several issues are expected throughout the development of a new class of cancer compounds, there are some key issues and risks specific to ABT-518 to be addressed during the transition period:

#### 2.2.1. Formulation/Drug Supplies

Nominal drug formulation work will be done during the transition stage of development. Preliminary work has shown that drug substance in a capsule, when taken with food, will provide an adequate PK profile but larger doses may be required. The lack of formulation optimization during transition will contribute to a 6-8 month gap prior to the start of Phase II.

#### 2.2.2 Toxicology

The safety profile will need to be conducive to chronic administration in cancer patients. In screening studies, ABT-518 did not exhibit significant effects in genotoxicity, clastogenicity, cytotoxicity and ligand binding assays. In animal models, no significant CNS effects were produced by ABT-518 and the compound exhibited an improved acute cardiovascular safety profile relative to ABT-770. ABT-

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518 was well tolerated in rats treated for up to four weeks and in a small number of monkeys treated for two weeks. The maximum tolerated dose in both species was greater than the highest dose tested (100 mg/kg/day). Changes produced by ABT-518 included an increase in liver weight in rats and a slight decrease in food intake in one of two monkeys tested. No joint toxicity has been observed in either rats or monkeys. However, hypertrophy seen in the growth plates of rats needs further assessment. This hypertrophy is not believed to be similar to that reported with marimastat (subphyseal fractures, fibroplasia of the musculotendinous insertion sites, and clinically evident impairment of motion) and is seen in Gel B knockout mice without resulting deformities. Based on AUC values from preclinical efficacy and safety studies, ABT-518 has a larger therapeutic window than ABT-770 in rodents. In GLP toxicity studies it will be important to assess the occurrence of phospholipidosis as this was a significant finding with ABT-770.

The relationship of tissue metabolite accumulation to long-term safety is not known but is suspected to be important. Metabolites are produced following multiple oral doses of ABT-518 in rats and monkeys, with the absolute and relative amounts being gender and species dependent. However, accumulation of metabolites in tissues of treated rats and monkeys was far less for ABT-518 than for ABT-770. Five major metabolites of ABT-518 (selected by concentration and potential reactivity) have been synthesized for analytical method development. The toxicology program will include an assessment of metabolite production and toxicity. These metabolites will also be analyzed in the Phase I study. Analysis of this many metabolites is not a trivial undertaking and it is hoped that this number can be reduced once the human metabolite profile is better understood.

### 2.2.3. Clinical

The objective of the clinical program during Transition is to show that the safety and pharmacokinetic profile of ABT-518 in cancer patients are similar to or better than those of the competitor compounds. A prolonged exposure period will be required to assess the potential for joint toxicity in view of the MMPi competitor experiences. A secondary objective will be to establish a dose for the Phase II program.

Four critical questions need to be answered to recommend further development:

1. Can target trough plasma concentrations of 0.1 µg/ml be achieved after oral administration of ABT-518?
2. Can ABT-518 be administered once or twice a day?
3. Can ABT-518 be administered chronically in cancer patients with an acceptable safety profile?
4. Will ABT-518 produce the joint stiffness that has been observed with other MMPis in development?

This transition assessment will not include a single-dose study in healthy volunteers. The primary reason for a normal volunteer Phase I single-dose study is to provide single-dose pharmacokinetics<sup>1</sup> (PK), thus allowing the rapid selection of a starting dose for the Phase I multiple-dose study. This was true for ABT-839 (FTI) and ABT-510 (TSP). The questions that need to be answered for ABT-518 will require multiple dosing and are unlikely to be identified in a single-dose study. In addition, the competitor MMPi, marimastat, demonstrated differences in PK between normal volunteers and

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cancer patients, thus making it doubtful that the single-dose data would predict a starting dose in cancer patients.

However, if non-cancer indications are pursued, a Phase I SD/MD study in healthy volunteers may be required. Ophthalmologic indications such as macular degeneration or diabetic retinopathy would likely be topically dosed and would only require evidence of minimal systemic exposure. Indications requiring systemic exposure such as multiple sclerosis or rheumatoid arthritis would likely require additional Phase I studies in healthy volunteers.

It is known that joint toxicity is both compound-dependent and dose-dependent, and with broad spectrum MMPs it has been seen only after four weeks of dosing or later. At lower doses it took more than eight weeks for the toxicity to be seen. While reports of joint toxicity during the initial portion (28 days) of the study are unlikely, this dose-limiting toxicity will be assessed during the extension portion of the study.

The planned multiple-dose study (and its extension) will establish ABT-518 pharmacokinetics in patients, and more importantly will assess the safety profile following a minimum of 28 days administration. The duration of the study and its extension will be sufficient to project the safety risks for chronic use of this class of cytostatic agent. The study objectives will be to:

- Identify the dose that will provide acceptable systemic exposure after oral administration (plasma trough concentrations of 0.1 µg/ml).
- Assess acute and multiple-dose safety.
- Identify potential doses for the Phase II program.

### 3. Transition Program

In order to achieve the above objectives and assess the ABT-518 specific attributes and issues, the Transition Team will carry out the activities described below:

#### 3.1 Bulk Drug Synthesis

- 100 grams of non-GMP drug was delivered 12/99 by Chemical Sciences for selection of ABT-518 as a candidate.
- 1.7 kilograms of non-GMP material was delivered 6/00 for the one-month animal toxicity studies.
- 3.8 kilograms of GMP material was delivered 6/00 for the Phase I multiple-dose study.
- 10 kilograms of GMP material will be delivered 3Q01 to complete the Phase I trial with extensions and initiate Phase II preparation. This campaign might be larger depending on Chemical Sciences process initiatives.

#### 3.2 Formulation Activities

- Available "drug in a capsule" data have demonstrated >63% bioavailability in fed dogs. Based on these data, the Transition Team will proceed into Phase I with drug substance in a capsule

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administered with food. Capsule strengths will be 25 mg and 200 mg to provide dosing flexibility with minimal patient inconvenience.

- No further formulation work is planned during the transition phase beyond preliminary experiments of limited scope. If a Go decision is made at the end of Phase I, a minimum of 9 months (3-4 months for bulk drug delivery and 6-8 months for PARD) will be needed to support Phase II studies. These activities will depend on the PK and safety results seen in the Phase I study and may be accelerated at risk based on preliminary results.

### 3.3. Toxicology Program

The toxicology program has been designed to provide the data required to support the Phase I clinical program. The Toxicology plan includes the following studies:

- Acute studies in rodents
- 1-month repeat dose studies in rats and monkeys
- Genotoxicity evaluation for mutagenic and clastogenic potential

One-month toxicology studies were started 6/00 with results available 9/00 to support the first-in-man multiple-dose study. On the basis of these studies several key safety determinations will be made: 1) identification of target organ toxicities, 2) determination of reversibility of tissue changes with drug discontinuation, 3) characterization of the contribution metabolites have on toxicity, and 4) recommendation for acceptable starting dose for human studies.

Challenges include: 1) measurement of five primary metabolites in plasma (and possibly tissues) as well as evaluation of their genotoxicity potential in a selection of mutagenicity and clastogenicity assays, and 2) decrease in plasma drug concentrations with repeated dosing may be a limiting factor for attaining target organ toxicity. Although autoinduction of ABT-518 metabolism is a likely cause, other possibilities exist, including formulation limitations and changes in absorption. These issues will be further characterized in the one-month studies.

### 3.4. Metabolism Program

Metabolism studies will continue throughout the transition period. Specifically, ongoing studies will focus on confirming the structure of circulating metabolites identified by co-chromatography and other, as yet unidentified, circulating plasma and tissue metabolites that were present in the 1-month non-GLP toxicology studies. Pending the successful synthesis of radiolabeled ABT-518, a mass balance and excretion study will be conducted to confirm quantitative recovery of dosed radioactivity and to determine the ultimate elimination products of ABT-518 *in vivo*. Basic *in vitro* studies will also be undertaken with ABT-518 and available metabolite standards to explain the metabolic disposition of ABT-518 in toxicological models (rat and/or monkey). Similar *in vitro* experiments in human models will be conducted in an attempt to describe likely metabolic disposition of ABT-518 and its metabolites in humans. These studies will be available prior to the initiation of the Phase I multiple-dose study.

### 3.5 Regulatory

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The Phase I multiple-dose study will be conducted ex-US without an IND. The Phase II program is planned to be conducted under a US IND. To facilitate initiation of the Phase II program, a small (14 patients) Phase I study will be submitted to the FDA to open the US IND. The IND will be opened 2Q01, prior to completion of the multiple-dose study and will facilitate the Phase II program by early identification of issues/requirements raised by the FDA. Opening the IND in 2001 could potentially reduce the development gap between Phase I and Phase II.

An additional benefit of this approach would be to establish a good working relationship with the FDA Oncology Division.

### **3.6. Phase I Multiple-Dose Study in Cancer Patients**

The goals of the multiple-dose study in cancer patients are to determine the maximum tolerated dose (MTD), and evaluate the safety and pharmacokinetics of escalating doses of ABT-518. In the study 6-10 cohorts of cancer patients will be treated with a course of ABT-518, with a course being defined as 28 days of treatment. Each cohort will consist of a minimum of 3 patients diagnosed with refractory cancer. The starting dose for the 1<sup>st</sup> cohort will be determined by results of the one-month rat and monkey toxicity studies. Subsequent cohorts will be escalated by 25% - 100% dependent on the PK profile (parent and metabolites) and observed toxicity. Escalation will discontinue once dose-limiting toxicity occurs in 2/3 of patients in a cohort. This dose will become the MTD. An additional 6 patients will be exposed to ABT-518 at the previous dose level to acquire additional safety data.

Patients who wish to continue treatment with ABT-518 will be enrolled into an extension study, where they will be treated until dose limiting toxicities are reported or disease progression occurs.

#### **3.6.1. Primary Objectives of the Study:**

- Identification of an MTD.
- Assessment of the pharmacokinetics of the parent compound and achievement of a trough plasma concentration of 0.1 µg/ml.
- Assess clinical dosing frequency of QD and BID.
- Assess the safety profile after multiple doses in cancer patients with particular attention to joint toxicity.
- Recommend a Phase II dose(s).

#### **3.6.2. Secondary Objectives:**

- Evaluate the relationship of MTD to biologically significant inhibition.
- Assess a biomarker of activity in relation to drug exposure.
- Evaluate the metabolite profile in patients.

#### **3.6.3. Decisions Based on Multiple-Dose Study Results**



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At the completion of the Phase I multiple-dose study a Go/No Go decision will be made based on the safety and pharmacokinetic data. If targeted trough concentrations (0.1 µg/ml) after oral dosing with ABT-518 cannot be achieved, or if either an excessive dose (greater than 2 grams) or dosing frequency of more than BID is required, a recommendation on program discontinuation will be made. If results reveal considerable toxicity during the chronic administration of the targeted therapeutic dose, continued development of ABT-518 will be considered on the basis of potential benefit/risk ratio and the status of competition at that time. Evidence of joint toxicity reported during the study will be evaluated against what is known about the competitors' MMPi's.

#### **4. Backup Strategy**

From an intellectual property perspective, the MMP inhibitors field is quite mature. Over the past 10 to 15 years a steady stream of patent applications covering a range of structural classes have been published. Novel compositions of matter, particularly within the succinyl and biaryl hydroxamate classes, are now scarce. The biaryl ether retrohydroxamate class of MMP inhibitors provides Abbott with a patent niche within this very crowded field. The attributes and liabilities of this class have been fully explored by the Project Team; more than 390 retrohydroxamates were synthesized and extensively characterized over a 2-year period. While exceptions are always possible, it seems unlikely that the properties of ABT-518 can be vastly improved upon through further SAR within this series. Backup compounds to ABT-518 could be readily identified, yet they are apt to possess very similar properties. The opportunity to pursue other lead structures, generated through NMR screening or by other means, remains as a viable option, yet these endeavors must be viewed relative to other activities within Cancer Research. At this time the Project Team is applying no further effort to the discovery of novel MMP inhibitors.

#### **5. Post Transition**

The objective of the transition process is to conduct only those activities that are necessary to reach a Go/No Go decision for full development, thus minimizing the cost of early development. As such, once a Go decision is made following the Phase I program, there will be a delay of 6-8 months before initiating Phase II. This would be the time required to complete the necessary bulk drug synthesis, formulation activities, and regulatory preparation in order to proceed with the Phase II program. This gap could be minimized by resuming critical activities in support of Phase II prior to completion of the Phase I studies.

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#### 6. Timeline/Milestones

|  | <u>Initiation</u> | <u>Completion</u> |
|--|-------------------|-------------------|
| • Bulk Drug Delivery (1.7 kg non-GMP)            | Mar 00            | Jun 00            |
| • Toxicology                                     | Jun 00            | Oct 00            |
| - One-month rat                                  | Jun 00            | Sep 00            |
| - One-month monkey                               | Jun 00            | Sep 00            |
| - Genotoxicity & acute studies                   | Jun 00            | Aug 00            |
| • Go/No Go Decision Preclinical Safety           | Sep 00            | Sep 00            |
| • Bulk Drug Delivery (3.8 kg GMP)                | May 00            | Jun 00            |
| • Formulation Development<br>& Clinical Supplies | Jun 00            | Sep 01            |
| • Phase I MD ( 28 days)                          | Nov 00            | Dec 01            |
| • Pre-IND Meeting with FDA                       | Feb 01            | Feb 01            |
| • Submit US IND                                  | Apr/01            | Apr/01            |
| • Initiate US Phase I                            | Jun 01            | Jun 01            |
| • Bulk Drug delivery (10.0 kg GMP)               | Jun 01            | Aug 01            |
| • Go/No Go Phase II                              | Dec 01            | Dec 01            |
| • Initiate Phase II                              | Apr 02            | Apr 02            |

#### 7. Transition Costs (\$MM)

|  | <u>2000</u> | <u>2001</u> |
|--|-------------|-------------|
| Clinical Program *                       | 1.8         | 2.2         |
| CMC (PARC, Chemical Sciences, Discovery) | 2.3         | 2.3         |
| Drug Safety                              | 1.8         | 2.0         |
| Other support costs †                    | 0.1         | 0.2         |
| <b>Total</b>                             | <b>6.0</b>  | <b>6.7</b>  |

\* Clinical Program = Grants, Data Mgt/STATS, Venture Management

† Other Support Costs = Regulatory Affairs, RQA, Medical Services

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*August 2000*



# **Deposition Exhibit No. 10**

**D's Exhibit 827**



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ABT - 518

## Descriptive Memorandum

*February 2001*

Abbott Laboratories

ABT 0004032  
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**MMPi****Overview**

Abbott's Matrix Metalloproteinase Inhibitor (MMPi) program represents a novel therapeutic class, with the potential to alter the way that cancer is treated by preventing or modifying disease progression and/or metastases. This more "chronic" approach to therapy has the potential to transform cancer into a disease that patients live with, much like the effect of HIV protease inhibitors on patients with AIDS. It also has the potential to expand the cancer market significantly by increasing the average length of treatment and expanding the pool of patients eligible to receive therapy.

The MMPs comprise a family of enzymes that degrade a wide range of matrix protein substrates. High expression of these enzymes occurs in cancer and is associated with the ability of tumors to grow, invade, develop new blood vessels and metastasize.

MMP inhibitors (MMPis) may suppress the progression of tumors by several mechanisms:

- Suppress invasion/metastasis by blocking the membrane traversal and access to blood/lymphatic vessels
- Blocking the remodeling of extra-cellular matrix in the vicinity of primary tumors to prevent stroma-bound growth factors from stimulating tumor growth
- Blocking angiogenesis by preventing the proliferation and migration of endothelial cells and neovascularization of tumor.

Experimental evidence suggests that gelatinase A and gelatinase B are particularly important in tumor progression, consequently the project team has targeted gelatinase selective inhibitors for the treatment of cancer. Another reason for targeting highly gelatinase selective MMP inhibitors relates to the side effect profile exhibited by broad-spectrum agents like marimastat. Chronic administration of marimastat causes a dose-limiting side-effect characterized by severe joint pain and stiffness. Since these joint effects may be mediated by inhibition of other MMPs like fibroblast collagenase, highly gelatinase selective agents may be efficacious without producing dose-limiting side effects.

The MMP selectivity profile exhibited by ABT-518 distinguishes it from competitor's compounds. ABT-518 possesses sub-nanomolar inhibition potencies versus both gelatinase A and gelatinase B and is substantially more selective for the inhibition of the gelatinases over fibroblast collagenase than marimastat and prinomastat. Despite its high selectivity, ABT-518 demonstrates antitumor activity equal or superior to prinomastat. Inhibition of tumor growth is dose dependent in both syngeneic and xenograft models. ABT-518 is also effective in blocking vessel formation in a mouse model of angiogenesis. ABT-518 is a stable crystalline solid which can be synthesized in six steps (25% overall yield) from commercial starting material.

ABT-518 gives rise to sustained plasma concentrations following single oral dosing in monkeys, dogs and rats. Bioavailabilities range between 68 and 93% depending on formulation and species. Several metabolites are produced after repeated oral dosing of ABT-518, although their relative amounts varies with gender and species.

ABT-518 displays no meaningful effects in genotoxicity, cytotoxicity and ligand binding assays and its cardiovascular effects in dogs are unremarkable. ABT-518 produces no significant toxic effects in rats treated with 100 mg/kg/day over 28 days. Plasma concentrations generated by ABT-518 in these studies are at least 20-fold higher than those necessary to produce efficacy in cancer animal models. ABT-518 is therefore a compelling development candidate with the potential to

demonstrate antitumor effects superior to the MMP inhibitors currently undergoing clinical trials. Phase 1 clinical trials in cancer patients began March 2001.

#### *The market*

Currently, cytotoxic agents represent the largest, and fastest growing, class of oncology agents by sales volume. The following chart summarizes the value of the current oncology market.

**Global Sales by Market Segment (\$ MM)**

|            | 1996 Sales | 1997 Sales | 1998 Sales | 1999 Sales (est) | CAGR '96-'98 |
|------------|------------|------------|------------|------------------|--------------|
| Hormone    | 4,414      | 4,784      | 4,884      | 5,000            | 5.2%         |
| Cytotoxic  | 4,278      | 5,212      | 6,268      | 7,300            | 21.0%        |
| Adjunctive | 3,367      | 3,651      | 4,166      | 4,900            | 11.2%        |
| Total      | 12,059     | 13,647     | 15,318     | 17,200           | 12.7%        |

Source: Datamonitor

**Sales by Region (\$ MM)**

|       | 1996 Sales | 1997 Sales | 1998 Sales | 1999 Sales (est) | CAGR '96-'98 |
|-------|------------|------------|------------|------------------|--------------|
| US    | 5,564      | 6,276      | 7,422      | 8,500            | 15.5%        |
| Ex-US | 6,495      | 7,370      | 7,896      | 8,700            | 10.3%        |

Source: Datamonitor

Cytostatic agents have the potential to alter the way cancer is treated and presents opportunities for fundamentally new ways of approaching the disease. This cytostatic market does not yet exist, though success of more cytostatic "like" treatments, such as hormonal therapies for prostate and breast cancer, suggest that the market potential for cytostatic agents could be significant.

The ultimate commercial and clinical success of the MMP1 will depend on the clinical benefit this product provides in key cancer types compared with current best therapy. These can be benefits provided by dosing this agent in addition to current therapy and/or as an alternative to best therapy, or as a new component of best therapy. All currently available products, including the market leaders such as Taxol, have significant shortcomings in their profiles.

However, as novel therapy, MMP1s will probably be adopted initially as add-on the current chemotherapy. As benefits are proven and clinical experience is gained, these agents may be used in earlier stages of cancer and/or in conjunction with surgery or radiation to prevent the progression of any microscopic disease that remains.

The clinical targets identified for this compound include late stage pancreatic cancer, late stage NSCL cancer (on-label), with late stage ovarian and breast cancer as additional cancer types where efficacy has been demonstrated, but not filed. Other cancer types this compound may be efficacious in include SCL, colorectal, bladder, stomach and prostate. Targets will be refined as we know more about this compound's in-vivo activity.



The following tables summarize the key marketed competitive products by indication (US data only):

| Late Stage Breast              |       |
|--------------------------------|-------|
| Product                        | Share |
| Cyclophosphamide/Cytoxan/BMS   | 18.7  |
| Doxorubicin/Adriamycin/P&U     | 17.11 |
| Docetaxel/Taxotere/RPR         | 16.25 |
| Paclitaxel/Taxol/BMS           | 16.11 |
| Trastuzumab/Herceptin/Genetech | 11.26 |

| Late Stage NSCL             |       |
|-----------------------------|-------|
| Product                     | Share |
| Carboplatin/Paraplatin/BMS  | 50.32 |
| Paclitaxel/Taxol/BMS        | 44.14 |
| Vinorelbine/Navelbine/Glaxo | 22.78 |
| Gemcitabine/Gemzar/Lilly    | 22.14 |
| Cisplatin/Platinol/BMS      | 11.28 |

| Late Stage Ovarian         |       |
|----------------------------|-------|
| Product                    | Share |
| Paclitaxel/Taxol/BMS       | 47.11 |
| Carboplatin/Paraplatin/BMS | 45.42 |
| Topotecan/Hycamtin/SKB     | 22.54 |
| Dox SL/Doxil/AIza          | 9.14  |
| Cisplatin/Platinol/BMS     | 7.58  |

| Late Stage Pancreas      |       |
|--------------------------|-------|
| Product                  | Share |
| Gemcitabine/Gemzar/Lilly | 78.5  |
| 5-FU/Efudex/ICN Pharma   | 21.0  |
| Leucovorin/              | 10.7  |
| Cisplatin/Platinol/BMS   | 4.72  |

#### *Compounds in Development*

The MMP inhibitor field is competitive. More than 30 firms have filed patents claiming small molecule MMP inhibitors over the past 5 years, and several companies have compounds in advanced clinical development. Abbott's compound may be 3<sup>rd</sup> or 4<sup>th</sup> to market and will have to demonstrate a competitive advantage to gain the share necessary to support the clinical development of this compound. Companies with compounds in advanced clinical development for the treatment of cancer include Agouron/Warner Lambert/Pfizer, British Biotechnology/Schering Plough and BMS and are listed below. Other companies are targeting this mechanism for arthritis.

#### MMPis in Clinical Development for Cancer

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| Compound    | Company                                  | Comments   | Phase |
|-------------|--|--|-------|
| Marimistat  | BritishBiotechnology/<br>Schering Plough | Broad spectrum, dose limiting toxicity. Activity seen in gastric cancer, but negative results in pancreatic.                         | III   |
| Prinomastat | Agouron/<br>Warner Lambert/<br>Pfizer    | Moderate gelatinase selectivity, dose limiting toxicity. May be dosing sub-optimally to avoid toxicity. Efficacy data not available. | III   |
| BMS 275291  | BMS                                      | Broad spectrum, joint effects seen in Phase I studies.   | II    |

Bayer recently dropped development of BAY 12-9566 due to concerns about potential toxicity. Recent results from a study with marimistat in pancreatic cancer, where adding marimistat to Gemzar resulted in no survival advantage, has led to speculation that MMPs may be more applicable in less aggressive cancer types or earlier stages of the disease. Alternatively, it could be a reflection of the inability to examine higher doses of marimastat due to joint effects.

The joint effects produced by the compounds listed above almost certainly preclude their long-term use, limit compliance and reduce optimal efficacy. Any MMP inhibitor that lacks these side effects will possess a substantial competitive advantage. The musculoskeletal effect produced by marimastat and prinomastat in cancer patients is typically described as arthralgia, myalgia and tendinitis, which occurs predominately in the upper limbs. While mild cases respond to analgesics, interrupting therapy for a period of approximately 2 weeks is necessary when the condition is less well tolerated.

Although Abbott's timing to market is not optimal, the shortcomings of the competitive products provide an opportunity for a compound with an improved SE or efficacy profile. Current animal models seem to predict Abbott's compound is superior to those currently in clinical trials, and has the potential to be best in class.

#### Product profile

The objective of a product profile at this time in the product's development is to provide a target for the types of attributes that will be required to be commercially successful. This profile is based on market research with oncologists and consultation with opinion leaders. This profile will continue to be refined as more is known about this product's profile, development of competitive products and the market continues to evolve.

|          | Base   | Optimal   |
|----------|--|---|
| Efficacy | ABT-518, alone or in combination with best therapy, provides at least one of | Provides more than one of the efficacy benefits outlined. |

|                       |   |  |
|-----------------------|---|--|
|                       | <p>the following benefits in at least one solid tumor type:</p> <ul style="list-style-type: none"> <li>Increased survival</li> <li>Tumor regression</li> <li>Improved quality of life</li> <li>Increased time to tumor/disease progression</li> </ul>             |  |
| Competitive advantage | ABT-518 will need to demonstrate a clinically significant advantage in efficacy (see parameters above) or additive synergistic activity with current/competitive agents or clinically significant advantage in side-effect profile relative to other MMPi agents. | Same   |
| Administration        | Convenient administration relative to competitive agents.   | Same plus reimbursement in US market.  |
| COGS                  | A finished cost of goods that is consistent with at least an 80% standard manufacturing margin.   | A finished cost of goods that is consistent with at least a 90% standard manufacturing margin. |

#### Marketing overview

**Product Usage:** Physicians have indicated that they would use MMPi initially in their more refractory patients, as follow-on or add-on to current best therapy (chemo or surgical). With experience and clinical evidence, they would be willing to use these agents in earlier stages of the disease, where they perceived the greatest benefit to be. The MMPi was regarded as a maintenance therapy to be used in early disease or after primary therapy as a prophylactic process to prevent the spread of malignancy.

**Product Benefits/Efficacy:** Physicians are looking for improvements in time to tumor progression and prevention of metastases with cytostatic agents. The MMPi mechanism has more recently been implicated as having an even more active role in cancer pathogenesis, from preventing primary tumor growth to anti-angiogenic properties. Positive results from competitive agents, such as marimistat in gastric cancer, provides proof of principle for this mechanism.

**Side Effects:** The proposed safety profile of MMPi (excluding joint toxicity) may enhance usage, as the dose limiting toxicity profiles of most of the other available agents has established a much lower hurdle for demonstrating a preferred profile. However, as chronic therapy, MMPi may have to demonstrate a cleaner profile than cytotoxic agents do to ensure compliance. As the 3<sup>rd</sup> or 4<sup>th</sup> MMPi to market, SE hurdles will be even higher for this compound. As a critical Go/No Go decision point, the joint toxicity of this compound will be evaluated in an expanded Phase I multi-dose study.

**Dosing:** Discovery is currently targeting an oral dosage form. In general, oral therapies are acknowledged by physicians and patients as being more convenient to the patient. Chronic oral dosing may also reduce overall costs, as infusion support products and personnel would not be required, enhancing pharmacoeconomic evidence.

**COGS:** Initial estimates on finished cost of drug suggest that drug costs will not be significant for this compound

*Off-label use:* Off label use accounts for between 30-60% of an oncology product's usage. Off-label use is driven by publication of clinical trial results in credible journals, listing in key compendia and/or a peer's experience with the product. Therefore, development spend for off-label use is considerably less than the spend required for regulatory approval of an indication. However, promotion of these off-label uses is limited.

*Competition:* As the 3<sup>rd</sup> or 4<sup>th</sup> MMPI to market, Abbott's compound will need to demonstrate a meaningful clinical advantage over compounds that are in more advanced development. Strict Go/No Go criteria will determine if the MMPI can meet these hurdles. If they cannot be met, the compound will not move forward.

*Development/Regulatory:* With a new class of compounds, there is not a clearly defined clinical development path or regulatory guidelines for reference. This hurdle is similar for all the competitive products, but increases the overall development risk profile for these agents. However, with several MMPIs in late stage development, Abbott can learn from their experience.

*Other Approaches:* Other "cytostatic" approaches may present a competitive threat if they are used as substitutes. Due to the complexity of the pathogenesis of cancer, it is more likely that these agents will be used in combinations, but incremental benefits may become more difficult to demonstrate as the number of products and approaches multiply. This will require additional studies, as these other classes become part of standard cancer treatment. However, this threat is not unique to this compound.

*Pricing:* The treatment of cancer is expensive, so there is the potential for a great deal of pricing flexibility in this market. However, as an oral therapy in the US market, there may be additional downward price pressure for this agent. There is also an increasing emphasis on cost-effectiveness studies that will need to be addressed in the development plan.

*Dosing:* Discovery is currently targeting an oral dosage form. In general, oral therapies are preferred by physicians and patients because of the convenience to the patient. However, this form may not be the best choice for some people who already have certain digestive system symptoms (vomiting, diarrhea, or severe nausea), cannot swallow liquids or pills, or cannot remember when or how many pills to take. Additionally, in the US market there are several unique factors that currently do not favor oral therapies. Novel oral therapies are not currently reimbursed by Medicare, a significant payer for the oncology patient population. Also, 40-60% of a community oncologist's income is generated through the administration of IV drugs. An oral therapy would not be a source of revenue to the physician.

#### *Clinical Studies*

Clinical studies across a wide range of solid tumors will be initiated, including but not limited to breast cancer, non small cell lung cancer, ovarian cancer, pancreatic cancer, etc...

Final indications pursued will depend from the results of the phase II studies.

**MMPI (ABT-518)**  
**2001 Plan Development Cost Summary**

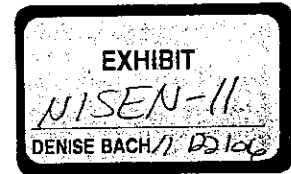
| Program Status                                  | 1999           |    |    |    | 2000                |    |    |    | 2001  |    |    |    | 2002  |    |    |    | 2003          |    |    |    | 2004           |    |    |    | 2005 |    |    |    | 2006 |  |  |  |
|---|----------------|----|----|----|---------------------|----|----|----|-------|----|----|----|-------|----|----|----|---------------|----|----|----|----------------|----|----|----|------|----|----|----|------|--|--|--|
|   | Q1             | Q2 | Q3 | Q4 | Q1                  | Q2 | Q3 | Q4 | Q1    | Q2 | Q3 | Q4 | Q1    | Q2 | Q3 | Q4 | Q1            | Q2 | Q3 | Q4 | Q1             | Q2 | Q3 | Q4 | Q1   | Q2 | Q3 | Q4 |      |  |  |  |
| Phase I   |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Phase II  |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Phase III                                       |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| NDA   |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| DDC   |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Launch  |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Major Development Activities and Costs          |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Clinical Program                                | Total Patients |    |    |    | Enrolled as of 8/00 |    |    |    | Start |    |    |    | End   |    |    |    | 2000 AGU Cost |    |    |    | 2001 Plan Cost |    |    |    |      |    |    |    |      |  |  |  |
| Multiple Dose in Cancer Patients                | 40             |    |    |    | "                   |    |    |    | 1Q/01 |    |    |    | 1Q/02 |    |    |    | \$300         |    |    |    | \$769          |    |    |    |      |    |    |    |      |  |  |  |
| IND Study                                       | 14             |    |    |    | "                   |    |    |    | 3Q/01 |    |    |    | 1Q/02 |    |    |    | "             |    |    |    | \$500          |    |    |    |      |    |    |    |      |  |  |  |
| Other Studies / EVR                             |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | "             |    |    |    | \$108          |    |    |    |      |    |    |    |      |  |  |  |
| Phase-I Center / PK                             |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$70          |    |    |    | \$65           |    |    |    |      |    |    |    |      |  |  |  |
| Venture Management                              |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$778         |    |    |    | \$754          |    |    |    |      |    |    |    |      |  |  |  |
| Data Management/Statistics                      |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$57          |    |    |    | \$118          |    |    |    |      |    |    |    |      |  |  |  |
|   |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$1,205       |    |    |    | \$2,314        |    |    |    |      |    |    |    |      |  |  |  |
| Chemistry, Manufacturing, and Controls (CMC)    |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Formulation / Analytical                        |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | 2000 AGU      |    |    |    | 2001 Plan      |    |    |    |      |    |    |    |      |  |  |  |
|   |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$546         |    |    |    | \$1,031        |    |    |    |      |    |    |    |      |  |  |  |
| Drug Safety Support                             |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Ongoing Drug Safety support                     |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | 2000 AGU      |    |    |    | 2001 Plan      |    |    |    |      |    |    |    |      |  |  |  |
|   |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$1,681       |    |    |    | \$2,125        |    |    |    |      |    |    |    |      |  |  |  |
| Other Support Costs                             |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    |               |    |    |    |                |    |    |    |      |    |    |    |      |  |  |  |
| Discovery                                       |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$1,447       |    |    |    | \$1,348        |    |    |    |      |    |    |    |      |  |  |  |
| Medical Affairs                                 |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$5           |    |    |    | \$20           |    |    |    |      |    |    |    |      |  |  |  |
| Regulatory Affairs / Research Quality Assurance |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$26          |    |    |    | \$39           |    |    |    |      |    |    |    |      |  |  |  |
| Other / In-licensing Fees                       |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$90          |    |    |    | \$123          |    |    |    |      |    |    |    |      |  |  |  |
| Total Program                                   |                |    |    |    |                     |    |    |    |       |    |    |    |       |    |    |    | \$5,000       |    |    |    | \$7,000        |    |    |    |      |    |    |    |      |  |  |  |

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11

# **Deposition Exhibit No. 11**

**D's Exhibit 828**



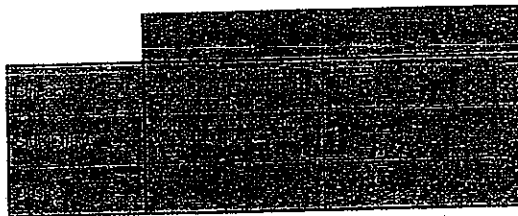
## Abbott Portfolio Review

March 7-9, 2001

- Project ABT-518
- Compound Matrix Metalloproteinase Inhibitor
- Presenter Perry Nisen
- Project Team Members  
A. Nabulsi (VH), T. Janus (MD), D. D'Amico (CPM)

### ABT-518

- ◆ Target indication: Solid tumors.
- ◆ Targeted unmet medical need: Cancer
- ◆ Target product profile vs. current gold standard:



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#### ABT-518

##### ◆ Key pre-clinical findings:

- Pharmacology
  - Potent and highly selective (gel-A and gel-B) MMP inhibitor
  - Anti-tumor activity seen in numerous murine cancer models
  - Inhibition of tumor growth is dose dependent
  - Blocks vessel formation in a mouse model of angiogenesis
- Pharmacokinetics / Metabolism in animals
  - Sustained plasma concentrations following single-dose in monkeys
  - Oral bioavailability between 68 and 93% in animals
  - Multiple metabolites are produced after repeat dosing in rats and dogs
- Toxicology
  - No meaningful effects in genotoxicity, cytotoxicity or ligand binding assays
  - No remarkable cardiovascular effects in dogs
  - Steatosis seen in high-dose rats two weeks after drug stopped

#### ABT-518

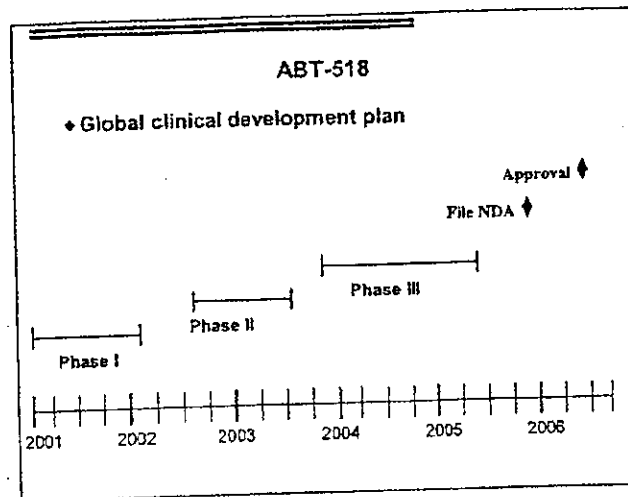
##### ◆ Chemistry and Manufacturing

- Drug substance
  - Six steps from commercial starting materials
  - 3-month turnaround time to manufacture
  - Manufactured at Abbott
- Drug product
  - Neat drug in a capsule (25 and 200 mg) for Phase I
  - Hand-fill or semi-automation at a third party manufacturing facility (Phase I)
  - Formulation development work will begin post Phase II Go/No Go decision

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ABT-518

♦ Clinical development budget

| Phase        | Funding (\$MM) |
|--------------|----------------|
| Pre-Clinical | 5              |
| Phase I      | 12             |
| Phase II     | 47             |
| Phase III    | 78             |

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### ABT-518

#### ◆ Phase I study:

Multiple-dose study in patients with advanced cancer

##### - Objectives

- Establish safety profile
- Determine the maximum tolerated dose (MTD)
- Assess PK
- Determine Phase II dose

##### - Design

- 28 days + extension
- Single-dose of drug administered on Day 1; resume dosing (daily) on Day 4
- Approximately 40 patients; 3 patients per dose
  - At least 6 or more patients at MTD to collect additional safety information
- Doses: 25, 50, 100, 200, 400, 800, 1200, 1600, 2000 mg/day

### ABT-518

#### ◆ Phase I plan:

##### IND Study

##### - Objectives

- PD-guided Phase II dose selection
- Long-term safety

##### - Design

- Multiple dose escalation study
- Assess MMP activity in accessible tumors
  - Melanoma
  - Head and Neck Cancer
- Approximately 20 patients

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**ABT-518**

**◆ Phase II development plans:**

- 3 Studies
  - 3 Tumor types as defined by Phase I and animal efficacy
  - 150 patients per study
- Dose finding
- Assess safety issues identified in Phase I
- Thirteen month duration

**ABT-518**

**◆ Phase III plan:**

- Demonstrate improvement in survival or TTP in combination with cytotoxic therapies

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| Strategic Summary  |
|--|
| <p align="center"><b>ABT-518</b></p> <p>♦ Key project strengths / positives:</p> <ul style="list-style-type: none"> <li>- Product attributes                             <ul style="list-style-type: none"> <li>• Highly selective for the inhibition of gelatinases A &amp; B</li> <li>• Very potent</li> <li>• No joint-toxicity expected</li> <li>• Potentially best in class</li> </ul> </li> <li>- Technology / Innovation                             <ul style="list-style-type: none"> <li>• Oral, once-a-day dosing</li> </ul> </li> <li>- Time to market                             <ul style="list-style-type: none"> <li>• Potential for fast-track approval</li> <li>• Launch 2006</li> </ul> </li> <li>- Business franchise strength                             <ul style="list-style-type: none"> <li>• Comprehensive oncology franchise</li> <li>• Synergies with HPD and ADD</li> </ul> </li> <li>- Other relevant points                             <ul style="list-style-type: none"> <li>• Competitors in class</li> <li>• Non-oncologic indications                                     <ul style="list-style-type: none"> <li>• Multiple sclerosis</li> <li>• Proliferative retinopathy</li> <li>• Arteritis</li> </ul> </li> </ul> </li> </ul> |

| Strategic Summary   |
|---|
| <p align="center"><b>ABT-518</b></p> <p>♦ Potential issues / Threats / Negatives:</p> <ul style="list-style-type: none"> <li>- Toxicity / side effects                             <ul style="list-style-type: none"> <li>• Metabolites that may accumulate over time</li> <li>• Potential mechanism-based drug interaction (CYP3A inducer-inhibitor)</li> <li>• Microvesicular and macrovesicular steatosis in rat study</li> </ul> </li> <li>- Manufacturing / cost of goods — No issues anticipated</li> <li>- Efficacy                             <ul style="list-style-type: none"> <li>• Data released from competitors may cast doubt on class</li> </ul> </li> <li>- Clinical recruitment problems                             <ul style="list-style-type: none"> <li>• Extensive protocol prohibited medications list</li> </ul> </li> <li>- Regulatory risk                             <ul style="list-style-type: none"> <li>• No precedent for cytostatic drug approval</li> <li>• Undefined clinical endpoints</li> <li>• Competitor data may pose additional development hurdles</li> </ul> </li> <li>- Technical risks — No issues anticipated</li> <li>- Other relevant issue                             <ul style="list-style-type: none"> <li>• No good models for selection of dose, regimen and responsive tumor types</li> <li>• PD marker selection</li> </ul> </li> </ul> |

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Strategic Summary

### ABT-518

♦ Key decisions:

- Important upcoming decisions
  - Transition team Go/No Go Phase II - 12/01
- Proposed budget (2001, and all years to launch)

| Year | R&D per year (\$MM) |
|------|---------------------|
| 2001 | 7                   |
| 2002 | 38                  |
| 2003 | 56                  |
| 2004 | 29                  |
| 2005 | 23                  |
| 2006 | 8                   |

Strategic Summary

### ABT-518

♦ Key decisions:

- Evaluate safety at multiple doses and dose regimens
- Dose and regimen selection for Phase II
- Tumor type selection for Phase II
- Clinical trial design to demonstrate efficacy

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| ABT-518  |  | Strategic Summary |
|--|--|-------------------|
| • Proposed action plans  |  |                   |
| - Manufacturing  |  |                   |
| • Initiate formulation work post Phase II Go/No Go   |  |                   |
| - Nonclinical  |  |                   |
| • Additional toxicology and metabolism studies are underway to explore the CYP3A and statosis issues |  |                   |
| - Clinical   |  |                   |
| • Measure metabolites in Phase I   |  |                   |
| • Assess bioactivity via PD markers in Phase I   |  |                   |
| • Hold a Pre-IND meeting with the FDA to discuss endpoints   |  |                   |
| - Contingency plan   |  |                   |
| • Pursue alternative indications   |  |                   |
| - Multiple schedule  |  |                   |
| - Proliferative mimicry  |  |                   |
| - Activity   |  |                   |

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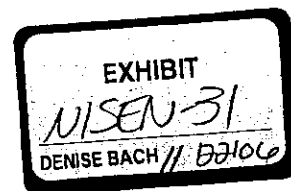
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31

# **Deposition Exhibit No. 31**

**D's Exhibit D\_GI**



## ABBOTT

### Pharmaceutical Products Division

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August 10, 2001

To: Perry Nisen D48J, AP30

Re: ABT-518

Below please find commentary on the results from the ABT-518 clinical trial, the status of the MMPI competition and an opinion on a path forward for Abbott's MMP inhibitor program. To summarize, the lack of clinical efficacy of competitors' compounds likely relates to their inability to maintain plasma concentrations above target levels, due to dose-limiting musculoskeletal effects. Based on the clinical data generated thus far, the exposure and toxicity profile of ABT-518 provides evidence that it may overcome these drawbacks. Completion of Phase I studies in cancer patients is recommended.

#### I. ABT-518 Clinical Results - Pharmacokinetics

Despite the limited number of patients analyzed thus far, the pharmacokinetics produced by ABT-518 appears to have met our objectives. The estimated plasma half-life (20 hours) is consistent with once daily dosing and the C<sub>max</sub> /C<sub>min</sub> ratio (1.8 to 6) [1, 2] is far smaller than that produced by prinomastat (30 to 55).[3] The mean trough concentration for the two patients given a 50 mg dose of ABT-518 was 380 ng/mL (760 nM), a value within the range of our original target concentrations (see Section IV below). One concern based on preclinical animal studies was the possibility of ABT-518 inducing its own metabolism. While there is a trend towards lower AUCs on Day 22 versus Day 1, significant metabolic induction does not appear to be an issue for the 25 mg and 50 mg doses of ABT-518. It would be interesting to match ABT-518 exposure to patient gender, given the substantial differences that were observed in male and female rats preclinically.[4]

Based on the pharmacokinetic profile of one patient given a 25 mg dose over 22 days, metabolite exposure was low relative to parent drug, the highest metabolite to parent ratio being produced by the amine metabolite.[5] This is consistent with preclinical studies in rats and monkeys wherein "pharmacologic" doses of ABT-518 resulted in low metabolite to parent ratios.[6] It is important to recognize, however, that the analysis is not complete without assessment of the aryl sulfonic acid, a metabolite that was identified after development of the clinical assay.

#### II. ABT-518 Clinical Results - Toxicity Profile

The toxicity profile produced by ABT-518 is perhaps the single most important factor in deciding whether further development is justified. A summary of the SAEs observed during this study has been distributed however a determination as to whether these events were drug related is not yet available. Clearly, a decision on whether to propose additional studies with ABT-518 is contingent on these results.

Since abandoning the broad spectrum MMP inhibitor approach in 1997, we have argued that Abbott's gelatinase-selective MMP inhibitors would differentiate themselves from the competition by avoiding the joint toxicity "ceiling" seen with marimastat and prinomastat. Joint pain and tenderness was observed in approximately 33% of patients treated with a 10 mg dose of marimastat twice daily over 5 months.[7] Musculoskeletal effects significant enough to cause dose modification or discontinuation of treatment was

## ABBOTT

### Pharmaceutical Products Division

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seen in 27% of patients given a 25 mg dose of prinomastat twice daily over a 4 to 8 week period.[3] It is therefore quite encouraging that arthralgia & myalgia was not reported (as far we know) in any of the patients dosed with ABT-518 for as long as two months. While the number of patients is clearly too small to draw definitive conclusions, the lack of joint effects seen with ABT-518 is certainly suggestive that ABT-518 may indeed avoid the pitfalls of marimastat and prinomastat.

### III. Competition

Since it appears that the development of ABT-518 is largely predicated on the status of competitors' compounds, a review of the latest news on the leading inhibitors is provided below.

#### Marimastat

2001 ASCO abstracts:[8, 9]

- Marimastat (10 mg, po, bid) did not enhance overall survival or progression free survival of SCLC patients following first-line therapy. A slightly smaller study involving patients with glioblastoma multiforme produced the same result.
- In the SCLC trial, a significant percentage of the patients required either dose modification (20%) or withdrew from treatment (18%) due to musculoskeletal effects.

Independent of the negative results reported for marimastat at the 2001 ASCO meeting its development status is a bit cryptic. The IDdb investigational drugs database indicates that one study of marimastat in patients with resected pancreatic cancer is being continued since interim analysis did not meet the stopping criteria. Surprisingly, little information is available on the follow-up to study 145 involving marimastat in gastric cancer patients. One report mentioned that "long-term data (from study 145) demonstrated that patients treated with marimastat continue to show survival benefit compared with those receiving placebo", yet this study does not show up on the BBT website nor can it be found in clinical trial databases.[10] To complicate matters further, the latest issue of the *Journal of Clinical Oncology* includes a paper indicating that marimastat is as effective as gemcitabine in treating patients with unresectable pancreatic cancer, but is associated with a lower incidence of grade 3 & 4 toxicities.[11] According to BBT executives, the future direction of marimastat development is the "subject of ongoing discussion with Schering-Plough and with external experts".[10]

#### Prinomastat

2001 ASCO abstracts:[3, 12, 13]

- Phase III studies of prinomastat (in combination with paclitaxel and carboplatin) in NSCLC patients revealed no benefit in terms of overall survival; this was also true for a Phase III combination study in patients with metastatic hormone refractory prostate cancer.
- In a Phase II study of prinomastat in patients with progressive breast cancer, joint toxicity required treatment rest or discontinuation in 21% of patients given a 5 mg dose between 8 and 24 weeks and 27% of patients given a 25 mg dose between weeks 4 and 8.
- When asked what the future holds for prinomastat, *each* of the presenters responded with "assessment in earlier stage disease", yet *none* of the presenters were willing to define the nature of these trials; a go/no go decision on prinomastat will be made following these studies.

Pfizer discontinued the Phase III studies mentioned above in August of 2000 due to failure to meet primary efficacy objectives. However, patients having earlier stage disease in a second ongoing NSCLC trial are

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apparently continuing treatment. The IDdb database indicates that prinomastat is being assessed in four Phase II trials with two additional trials planned.[14] The design of these trials and whether they are all being conducted is not known.

**BMS 275291**

2001 ASCO abstracts:[15 – 17]

- Phase I studies of BMS 275291 in healthy volunteers and cancer patients indicated that it produces no joint effects different than placebo; BMS scientists continue to believe that this reflects the compound's lack of sheddase activity.
- Due to the presence of the free sulfhydryl group, BMS 275291 forms disulfides with other thiol-containing compounds. Pharmacokinetic analysis of BMS 275291 therefore includes "free" (unchanged parent) and "total" (parent measured after disulfide reduction). Unchanged parent is believed to be the pharmacologically active form.
- The stereocenter adjacent to the thiol group of BMS 275291 is partially racemized to the 60-fold less active (R,S,S) diastereomer in humans. This is apparently a recent finding and may explain why some of the trough concentrations reported in the ASCO abstract differ from those presented at the meeting (see, for example, abstract #301 (Gupta, E. et al.): trough concentrations produced by the 1,200 mg dose at steady-state: abstract = 398-567 ng/mL; poster = 158 ng/mL).
- While C<sub>max</sub> and AUC values of unchanged BMS 275291 increased in relation to dose from 600 to 1,800 mg, abstract #301 reports "no further increase in exposure between the 1,800 and 2,400 mg dose".
- The Phase II/III recommended dose is 1,200 mg, once daily. This dose produces unchanged parent trough concentrations of 158 ng/mL (Gupta study) which exceeds the gelatinase A/B IC<sub>50</sub>'s for BMS 275291 (20 and 14 ng/mL), but exceeds the IC<sub>50</sub> value only for gelatinase B (gelatinase A IC<sub>50</sub>: 261 ng/mL; gelatinase B IC<sub>50</sub>: 119 ng/mL).
- Dermal wound angiogenesis (measured following punch biopsy) was delayed in patients treated with BMS 275291, yet this response was not dose-dependent, consequently their Phase II/III dose (1,200 mg) was chosen based on plasma exposure.
- Phase II studies include NSCLC patients in combination with paclitaxel/carboplatin as well as Kaposi's sarcoma patients.

The BMS data presented thus far suggests that inhibition of MMP1 does not mediate joint toxicity. Whether TACE is the culprit is not known; it remains possible that MMP1-induced joint effects are due to inhibition of some unknown metalloproteinase. Regardless, several observations suggest that BMS 275291 may have more ills than originally thought. First, there are no published reports describing its preclinical efficacy in cancer animal models. Given that the compound has been described at a number of major meetings, this may indicate that its efficacy in animal models doesn't compare favorably to the other MMP inhibitors being developed. BMS 275291 is not highly protein bound (ca. 60%),[15] yet its pharmacokinetics are confounded by disulfide formation as well as racemization to a less active diastereomer. While the lack of joint effects clearly provides BMS 275291 with an advantage over marimastat & prinomastat, the report that doses higher than 1,800 mg did not cause an increase in plasma concentrations suggests that this compound may also suffer from a dose "ceiling", albeit for reasons different than its predecessors.[15]

**BAY 12-9566**

2001 ASCO abstracts:[18]

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|---|---|---|

- Follow-up to study of BAY 12-9566 in patients with ovarian cancer which was closed (based on data from pancreatic/SCLC patients) after enrolling 243 patients. Results from this study indicate that BAY 12-9566 (800 mg, po, bid) was neither beneficial nor detrimental. This provides evidence that MMP inhibition is not inherently harmful to cancer patients.

#### RS-130830

Roche's "selective" hydroxamate-bearing MMP inhibitor (RS-130830) was apparently discontinued due to musculoskeletal side effects.[19] It's MMP inhibition profile is similar to ABT-518, although TACE data for RS-130830 has not been reported.

#### IV. Why They Failed & Why We Might Not

A commonly cited explanation for the failure of marimastat, prinomastat and BAY 12-9566 in Phase III clinical studies has been the idea that MMPs do not play a significant role in mediating the progression of advanced stage solid tumors. Results from the Phase II studies being conducted with prinomastat in earlier stage disease will hopefully shed light on whether this is indeed the case. Given the likelihood that objective responses will not be observed in these studies, the establishment of a pharmacodynamic marker of MMP inhibition is very important for our MMPi development program (see Section V). Measurement of MMP proteolytic activity in human tumors would also be useful in identifying tumors types likely to respond to MMP inhibitors. To date the choice of which tumors to target for Phase III trials has been based largely on MMP expression, a read-out that is only an indirect measure of MMP function. This is a consequence of MMP proteolytic activity being regulated at several post-transcriptional steps including proenzyme activation and endogenous inhibitor (TIMP) complexation.

Independent of whether MMP inhibitors will perform better in earlier versus later stage cancers, there is evidence to suggest that marimastat, prinomastat and even BMS 275291 are inappropriate tools to answer this question in the clinic. Figure 1 illustrates why. This figure provides a comparison of target plasma trough concentrations based on preclinical efficacy studies, with trough concentrations achieved in cancer patients (you'll recall that this analysis was presented at the March 2000 DDC meeting and again at more than one MMPi Transition Team meeting). Based on our own studies and those in the MMPi literature, continuous exposure to MMP inhibitors is necessary for maximal efficacy in cancer animal models, thus the emphasis on maximizing *trough* concentrations. We have argued that the gelatinases are the most important MMPs for mediating tumor progression, consequently the mean  $IC_{50}$  value for gelatinase A and gelatinase B is used in Figure 1 (using either value alone produces that same conclusion). Taking prinomastat as an example, its "plasma binding-corrected" (PBCed)  $IC_{50}$  value in mouse plasma can be determined by multiplying its mean gel A/B  $IC_{50}$  value (0.048 nM) by a factor representing its "free fraction" which is based on its mouse plasma protein binding value determined *in vitro*. Prinomastat's protein binding in mouse plasma was determined to be 81.6% (0.816) therefore its free fraction is 0.184 (1 minus 0.816) and its PBCed gel A/B  $IC_{50}$  value in mouse plasma is 0.26 nM (1 divided by 0.184 times 0.048 nM). To determine the trough plasma concentration of prinomastat associated with preclinical efficacy, it was administered by osmotic minipumps in the B16 subcutaneous tumor growth model. Efficacy was observed at a continuous (trough) plasma concentration of 57 nM. For prinomastat there is therefore a 218-fold shift between the mouse PBCed gel A/B  $IC_{50}$  value and the plasma concentration associated with preclinical efficacy.

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Prinomastat's mean gel A/B  $IC_{50}$  value can be corrected for binding to human plasma in either of two ways, mathematically from its *in vitro* binding to human plasma (analogous to the calculations above) or from the fold-shift in gelatinase A potency determined in the absence/presence of 80% human plasma. By either measure, the PBCed gel A/B  $IC_{50}$  value for prinomastat in human plasma (0.22 nM or 0.17 nM) is not too dissimilar from its value determined for mouse plasma (0.26 nM). Applying the 218-fold shift from above to this human PBCed gel A/B  $IC_{50}$  value gives prinomastat's "target" efficacious trough concentration of 40-50 nM. Significantly, the trough concentration produced by a 25 mg dose of prinomastat in cancer patients is 47 nM as denoted by the green bar in Figure 1.[3] This represents an "upper limit" of prinomastat exposure since this dose is associated with significant joint toxicity.

The same analysis applied to marimastat produces a similar conclusion. Mouse plasma protein binding was not determined for marimastat, however low binding was observed in rat and monkey plasma (~10%) and a 3-fold shift was observed in its gel A potency in the presence of 80% human plasma. Efficacy in the B16 model using minipump delivery occurred at a marimastat concentration of 167 nM. Based on several clinical trials the trough concentration produced by a 25 mg, bid dose of marimastat is approximately 400 nM.[20, 21] As with prinomastat, this value is not much higher than the trough concentration associated with efficacy in animal models. Interestingly, a recent publication indicates that a 25 mg dose of marimastat given twice daily produces the same survival benefit as gemcitabine in patients with unresectable pancreatic cancer.[11] While this dose produced musculoskeletal effects in nearly half the patients, *most of whom required dosing holidays*, it provides significant evidence of clinical response to MMP inhibition.

As mentioned above, no definitive accounts of preclinical efficacy have been reported for BMS 275291 and we have not characterized this compound in our labs (its structure was revealed as we were winding down our program). The intrinsic potency of BMS 275291 for inhibition of the gelatinases (mean gel A/B  $IC_{50}$ : 33 nM) is inferior to the hydroxamate-based compounds and its binding to human plasma was reported to be 46 - 77% (mean = 60%).[15] Without a trough concentration associated with preclinical efficacy BMS 275291 cannot be definitively compared to the other compounds in Figure 1. It is important to recognize, however, that at least one study indicates that trough concentration produced by BMS 275291 in cancer patients peaks at 430 nM (1,800 mg dose); a 2,400 mg dose was associated with a smaller  $C_{max}$ , AUC(24h) and  $C_{min}$ . [15] Independent of whether this trend is reproduced in other studies, it does suggest that there may be an upper limit to the exposure of BMS 275291 in humans and that it too may be an inappropriate tool to establish the clinical utility of MMP inhibitors.

ABT-518 is more extensively protein bound than the other compounds in Figure 1 and its affinity differs between mouse and human plasma. It is 94.4% protein bound in mouse plasma and 99.2% protein bound in human plasma which gives rise to a PBCed gel A/B  $IC_{50}$  value of 11 nM (mouse) and 80 nM (human). Efficacy in the B16 model was observed at a trough concentration of 260 nM, 23-fold higher than its mouse PBCed gel A/B  $IC_{50}$  value. Applying this factor to the human PBCed gel A/B  $IC_{50}$  value (80 nM) provides what is arguably an upper limit to the target trough concentration in humans (1,800 nM). Alternatively, using ABT-518's fold shift in gelatinase A potency in the presence of 80% human plasma (53-fold; presumably a more realistic, "functional" correction factor), yields a target trough concentration of 760 nM. These values are in the vicinity of the trough concentrations produced by the 50 mg dose of ABT-518 in cancer patients and would likely be exceeded by slightly higher doses assuming that its exposure continues to be linear with dose. *The inability of competitors' compounds to substantially exceed target trough concentrations could potentially be overcome by ABT-518 if higher doses are absent of adverse effects.*

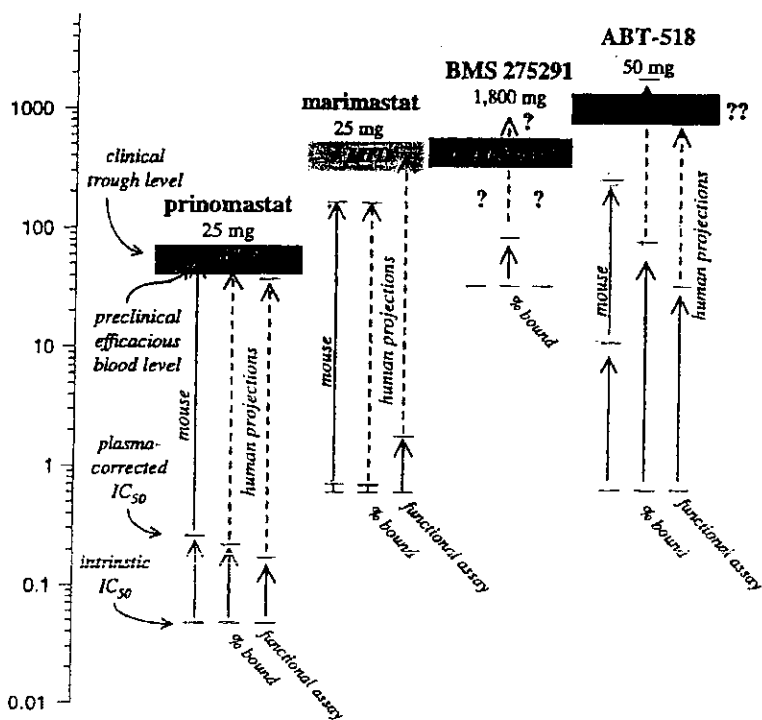
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**Figure 1.** Target versus clinical trough concentrations produced by prinomastat, marimastat, BMS 275291 and ABT-518.





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It is important to mention several caveats associated with the analysis presented above. For example, efficacy projections are based primarily upon data from a single model (B16 murine melanoma). Inhibitors were administered via minipump infusion in order to obtain steady state blood levels that were correlated with efficacy in the model. These steady state levels differ somewhat from the "trough levels" associated with efficacy generally reported in the literature, particularly in the case of prinomastat. Given the requirement for continuous exposure for maximal efficacy, we believe steady state levels provide a more realistic estimate of the required efficacious concentration than do trough levels, especially in the case of prinomastat where there is a large ratio between C<sub>max</sub> and C<sub>min</sub> after oral administration. There are also uncertainties about assessing the impact of plasma protein binding on efficacy as opposed to other factors such as tissue distribution. Given the relatively high affinity these inhibitors have for the target MMPs, the fraction bound in plasma may not accurately reflect the impact on activity. A functional assay of enzyme activity in the presence of plasma would seem to be a better approach and has been successfully pursued with human plasma; however, due to the presence of an unknown interfering substance, we have not been able to measure activity in mouse plasma. As mentioned above, we have no preclinical efficacy data for BMS. Rat and monkey plasma binding data were used in place of mouse and human for marimastat.

#### V. Path Forward

Based on the arguments raised above, the plan for further clinical studies with ABT-518 seems straightforward. First, the unresolved issues surrounding ABT-518's interrupted Phase I study need to be addressed. These include assessing the drug-relatedness of adverse events as well as the plasma concentration of the sulfonic acid metabolite. Second, it would be useful to have additional competitive intelligence on the clinical status of marimastat, prinomastat and BMS 275291, perhaps through Abbott's contacts with clinical oncologists familiar with the MMP inhibitors field. Most importantly, further Phase I studies should be undertaken to determine whether ABT-518 target plasma concentrations can be exceeded in the absence of dose-limiting toxicity. If target plasma concentrations cannot be achieved or if excessive metabolites are produced at these doses, development should be stopped. On the other hand, if ABT-518 crosses these hurdles, trials geared toward the assessment of efficacy should be initiated. It is important that Phase II studies include some measure of MMP activity so that evidence of functional MMP inhibition can be established prior to costly Phase III trials. *In situ* zymography detection of proteolytic activity in resected melanoma biopsies is one potential measure that could be used as a go/no go decision for ABT-518.[22] While conceptually appealing, validation of such a pharmacodynamic assay has not been achieved.

#### VI. Conclusion

To conclude, we feel that ABT-518 has the potential to be the first MMP inhibitor to demonstrate robust clinical efficacy. The points listed below provide a compelling argument as to why the development of ABT-518 should be continued.

- While the source of the MMPI-induced joint effects has not yet been resolved, the *in vitro* potency and selectivity of ABT-518 differentiates it from marimastat, prinomastat and BMS 275291.
- As a selective MMP inhibitor, ABT-518 exhibits efficacy in cancer animal models equivalent to competitors' compounds.
- Musculoskeletal toxicity limits the dose that can be examined by marimastat and prinomastat in cancer patients. Our analysis suggests that trough concentrations produced by these MMP inhibitors at their MTDs may be insufficient for clinical efficacy.

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- The encouraging human pharmacokinetic data produced by ABT-518, which avoids the large differences in C<sub>max</sub> and C<sub>min</sub> seen with competitors' compounds, suggests that trough concentrations substantially higher than its target levels may be achievable in the absence of limiting toxicity.

Please let me know if you would like to discuss these matters further.

#### VII. References:

1. Robert Carr Abbott internal email – 7-30-01; 6:20 PM; attached.
2. Robert Carr Abbott internal email – 7-31-01; 3:46 PM; attached.
3. Rugo, H. et al. *Proc. Am. Soc. Clin. Oncol.* **2001**, 20:48a (abstract 187).
4. A-291518 DDC document, page 26.
5. Robert Carr Abbott internal email – 6-8-01; 5:01 PM; attached.
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22. Ikeda M. et al. *Clin. Cancer Res.* **2000** 6: 3290-3296.

# ASCO 2001 MMPI Update

- Ten MMPI abstracts were presented
- Prinomastat, marimastat & Bay 12-9566 reported negative findings
- Possible reasons
  - Under dosing due to dose limiting toxicity (joint toxicity)
  - Inappropriate tumor selection
  - Inappropriate tumor stage (late vs. early)
  - Phase II development not done for prinomastat & Bay 12-9566
- BMS 275291 did not show joint toxicity in Phase I. Phase II studies are being initiated in NSCLC & Kaposi's sarcoma

# Prinomastat

- Non-small cell lung cancer
  - Combination with paclitaxel & carboplatin
  - No survival benefit
- Hormone refractory prostate cancer
  - Combination with mitoxantrone & prednisone
  - No effects on: PSA, progression free survival, overall survival
- Refractory metastatic breast cancer
  - Phase I/II single agent (n = 44)
- Grade 2 joint toxicity in above trials at all dose levels (5,10,25 mg bid)
- Studies in earlier stage tumors are still ongoing

# Marimastat

- Small cell lung cancer
  - Following response to 1<sup>st</sup> line therapy
  - 10mg vs. placebo
  - Total 155 patients
  - No benefit on progression free survival or overall survival
- Glioblastoma
  - Post surgery & radiotherapy
  - 10mg vs. placebo
  - Total 162 patients
- High dropout rate due to joint toxicity

## Bay 12-9566

- Ovarian cancer (stage III or IV)
  - 800mg bid vs. placebo
  - Study was discontinued prior to full enrollment due to lack of activity in pancreatic cancer and SCLC
  - No benefit on survival

## BMS 275291

- Phase I studies
  - Healthy volunteers (n = 40 males)
  - Cancer patients (n = 44)
- No joint toxicities (possibly due to lack of sheddase activity)
- No MTD through 2400mg / day
- Phase II plan
  - Non small cell lung cancer in combination with paclitaxel & carboplatin
  - Kaposi's sarcoma
  - Dose 1200 mg / day

# ABT-518 Phase I Multiple-Dose Study in Cancer Patients M00-235

- Patients enrolled to date
  - 25 mg / day 4
  - 50 mg / day  $\frac{3}{7}$
- Dosing duration up to 57 days
- Patients will continue dosing until disease progression or adverse events
- No musculoskeletal effects reported to date
- Next dose is 100 mg / day



# ABT-518 Development

## Recommendations

- Continue the ongoing Phase I study
  - Objectives
    - Determine target dose required to achieve target plasma concentration of 1-3  $\lambda$ M
    - Assess safety following chronic administration
  - Stop development if Grade 3 or 4 toxicities are attributed to doses at or below target dose
  - Stop for joint toxicity
  - If target dose is well tolerated, initiate a pharmacodynamic/proof of principle study with external funds (e.g., NCI-CRADA) and/or outlicense
    - Biopsy multiple melanoma, head and neck cancer, assay for gelatinase A/B activity

32

## **Deposition Exhibit No. 32**

**D's Exhibit 829**




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INTEROFFICE MEMORANDUM

---

TO: DAN NORBECK, JOHN LEONARD  
 FROM: PERRY NISEN  
 SUBJECT: ABT-518  
 DATE: 8/14/01  
 CC: STEVE FESIK, ~~STEVE DAVIDSEN~~, AZMI NABULSI

---

Dan asked me to send information that might convince him to revisit the decision regarding ABT-518 development. Attached are the following:

1. Memo from Steve Davidsen summarizing human pharmacokinetics and competitive intelligence
2. Primary pharmacokinetics data from Bob Carr
3. Recent reprints
  - o Zymography method to measure inhibition in tissues and a plasma assay (Bremer et al and Duivenvoorden et al)
  - o Clinical results of marimistat vs gemcytabine in Pancreatic ca (Bramhall + editorial)- evidence of activity
  - o Patients with gel A mutations have osteolytic/arthritis syndrome (Martignetti et al and Vu editorial) -a concern, but probably embryologic

Key points to consider:

- 5 patients were treated: three at 25 mg and two at 50 mg
  - o The PK is awesome: half-life 20 hrs, low  $C_{max}/C_{min}$  ratio, low metabolites. In contrast to the competitors', ABT-518 can readily maintain trough concentrations above the target level with once daily dosing (not enough patients treated long enough to determine if there are musculoskeletal effects). We are already at or near the target dose.
  - Adverse events were probably unrelated to drug:
    - One patient who developed venous thrombosis had a history of deep vein thrombosis and was treated with anticoagulants for a year. Anticoagulants were discontinued per protocol a month prior to initiating ABT-518

- Another patient who developed renal failure had a prior history of nephrectomy due to tumor invasion and had disease progression in the remaining kidney while on ABT-518
- Clinical trials with competitors' compounds indicates that none of them have the pharmacokinetic properties to enable consistent exposure at the target trough concentration. Furthermore, most of the studies were on patients with advanced, metastatic disease, unlikely to respond to this type of therapy. Notwithstanding, there is still some evidence for activity (see the marimistat study attached)

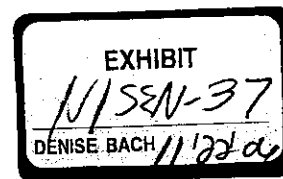
Completion of the phase I study would enable us to confirm that we can achieve target trough exposure safely and without musculoskeletal adverse events (~ 10 more patients). A small phase II study could be performed to establish proof of principle: patients with metastatic melanoma can be treated and biopsies assayed by zymography for inhibition of gel A and B as a pharmacodynamic measure. A go/ no go decision can be evidence-based: pharmacodynamics + delayed progression of existing metastases and inhibition of new metastases. This can be accomplished in a 40 patient study. A positive result would restore enthusiasm for the approach and a negative result would be a no go.

I have a meeting scheduled with the NCI to see if they will take over development. I am also having an outlicense package prepared.



## **Deposition Exhibit No. 37**

**D's Exhibit 830**



Gayle A  
Kirkpatrick /LAKE/GPRD/AB  
BOTT

09/23/2002 11:20 PM

To: Suzanne Lebold/LAKE/PPRD/ABBOTT@ABBOTT

Ake L Johansson/LAKE/GPRD/ABBOTT@ABBOTT,

cc: Thomas J Lyons/LAKE/PPRD/ABBOTT@ABBOTT, William

L Mathers/LAKE/GPRD/ABBOTT@ABBOTT

bcc

Subject: Re: Status of JH compounds/Divestment activities

Suzy,

In response to your email of 9/18 and information needed for an October review w/JH, I've polled the SA team and comments are as follows:

ABT-100: no outlicensing activities have been initiated per JHV.

ABT-518: See attached summary from John Fitz Gerald/JHV.

ABT-594: per Kevin and Jim Sullivan, this is not in current development and has NOT been publically communicated. ABT has focused on ABT-202, the back-up cmpd that has a more favorable pdt profile than ABT-594.

ABT-773: SM has assisted Ake with an outlicensing package

Let me know if any additional information is needed from the SA team



ABT518 Outlicense History.do

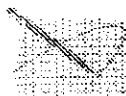
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Suzanne Lebold



Suzanne Lebold

09/13/2002 06:55 PM

To: Gayle A Kirkpatrick/LAKE/GPRD/ABBOTT@ABBOTT, Ake L  
Johansson/LAKE/GPRD/ABBOTT@ABBOTT

cc: William L Mathers/LAKE/GPRD/ABBOTT@ABBOTT, Thomas J  
Lyons/LAKE/PPRD/ABBOTT@ABBOTT

Subject: Status of JH compounds/Divestment activities

Gayle and Ake:

John Hancock has asked for a status update by 10/15 on the following compounds/outlicensing activities [per the contract, if we drop a compound, activities to realize the value of the asset]:

- ABT-100 [Gayle, I think that Jane is handling, can you please have her summarize planned activities]
- ABT-518 [Gayle, do we have a summary of who did evaluate 518- and conclude we have exhausted the supply?] I have some emails- but I don't know that it is complete- lets consolidate, ok?

Confidential

ABBT334838



- ABT-594 [Gayle- can you get an update from Kevin on this- still in 'development' or finally killed?, and do we have plans to outlisc?]
- ABT-773 [Ake- if we could update the process/where we are since the last update that you gave me, which Tom Lyons and I delivered (verbally) to JH on 8/30- thank you.]

Ake has a great summary for 773- timeline of events/who was contacted/status of each/next steps- which I think is appropriate for the others.

Please let me know if you have any queistons or need any additional information  
JH has a quarterly meeting with Tom Lyons and have asked us to provide this which we are contractually obligated to do. I have Michelle summarizing Article 4 of the agreement to show the rules of the road for each 'bucket' of compounds (and which compounds are treated in which mannet), as they all need to be treated slightly differently in terms of our obligation to 'realize the commercial value of the asset'.

Thank you in advance for your help- if you could please have summaries to me by Oct 11- we can get them to TOM before his meeting with JH-

Suzy

Tom- please confirm that this timing meets your quarterly update needs- thank you.

Suzanne A. Lebold, Ph.D.  
Senior Director, Scientific and Strategic Assessment  
Global Pharmaceutical Licensing and Business Development  
Abbott Laboratories  
Phone: (847) 937-1436 Fax: (847) 937-1771  
email: suzanne.a.lebold@abbott.com

**Abbott Laboratories**  
**Project Overview – ABT 518 - CLOSED**

**Title:** ABT 518 (previously in Ph I)

**Deal Type:** WW Out-license asset

**Background:** ABT 518 is a matrix metalloproteinase (MMP) inhibitor program which represents a novel therapeutic class with the potential to alter the way cancer is treated by preventing or modifying disease progression and / or metastases for solid tumors.

Abbott has contacted several companies with little interest to date.

**Origination:** Due to two other MMP failures in the market (therapeutic window did not occur prior to toxicity (caused severe joint pain) it was decided that this program was too risky. ABT 518 may have promise as the efficacy of has been shown to occur prior to toxicity.

**Patent:** Approx 2018

**Contacts:**

| Company           | Contact          | CDA        | Status   |
|-------------------|------------------|------------|--|
| Chiron            | Lauren Miller    | ??         | - No interest  |
| Duke University   | Dr. Herb Hurwitz | In process | - No interest on behalf of ABT; Duke wants for free                      |
| Paramount Capital | Jeffrey Solash   | ??         | - No interest on behalf of ABT; Paramount interested in option agreement |
| Salmedix          | Alan Rosenthal   | Yes        | - No interest  |
| Sunesis           | Akiko            | Yes        | - No interest  |

**Time Line / Action Plan:**

|           |  |
|-----------|--|
| August    | ABT valuation of asset                         |
| Sept      | ABT presentation of confidential data          |
| Sept      | ABT Terms sheet to perspective buyers          |
| Oct       | ABT selection of final partner / due diligence |
| Nov / Dec | Contract negotiation / execution               |

**Team Members:** John Fitz Gerald  
Jerry Wenker  
Jane Hoff-Velk  
Perry Nisen / Development  
Steve Fesik / Research

{DATE}

1 of 2

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**Abbott Laboratories**  
**Project Overview – ABT 518 - CLOSED**

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Legal / Others

**Additional Time:** Medium. (Preparation of slides for presentation, due diligence and contract negotiation).

**Deal Terms:**

- Upfront, development and regulatory milestones payable to ABT
- Royalties on net sales

**Other:**

- Spending to data and patent being looked into

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[DATE]

2 of 2

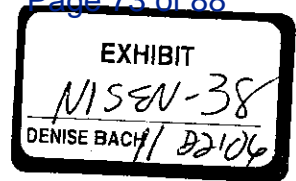
Confidential

ABBT334841

38

## **Deposition Exhibit No. 38**

**D's Exhibit 831**



Perry D Nisen

05/22/2001 06:27 AM

To: John M Leonard/LAKE/PPRD/ABBOTT@ABBOTT

cc:

cc:

Subject: ABT-518

Attached is a summary of findings on MMPIs from ASCO together with our recommendations for ABT-518. Should I send to Leiden or anyone else after you revise it?



ABT 518 ASCO - Plan May 21, 2001

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ABBT0064226

b7c

## **Deposition Exhibit No. 39**

**D's Exhibit 832**





Diane C  
Bronson/LAKE/PPRD/ABBOTT  
T

05/28/2001 09:03 PM

To: Diane L D'Amico/LAKE/PPRD/ABBOTT@ABBOTT  
cc  
bcc  
Subject: Re: ABT 518 Slides whoops

Diane,

Here are those slides.

I heard that Rob is leaving.

diane

----- Forwarded by Diane C Bronson/LAKE/PPRD/ABBOTT on 05/28/01 09:02 PM -----



Robert Hansen  
05/23/01 02:26 PM

To: Diane L D'Amico/LAKE/PPRD/ABBOTT@ABBOTT, Diane C  
Bronson/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: ABT 518 Slides whoops

----- Forwarded by Robert Hansen/LAKE/PPRD/ABBOTT on 05/23/2001 02:26 PM -----



Perry D Nisen  
05/22/2001 08:25 AM

To: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Robert  
Hansen/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: ABT 518 Slides whoops



ABT 518 ASCO - Plan May 21, 2001.

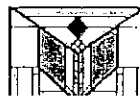
----- Forwarded by Perry D Nisen/LAKE/PPRD/ABBOTT on 05/22/01 08:24 AM -----



Perry D Nisen  
05/22/01 08:24 AM

To: Robert Hansen/LAKE/PPRD/ABBOTT@ABBOTT, Azmi A  
Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: ABT 518 Slides

Awesome- I just made some modest changes and will forward to the big dogs  
Robert Hansen



Robert Hansen  
05/21/01 06:51 PM

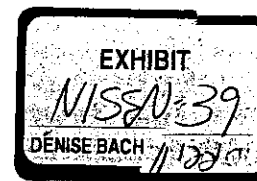
To: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT  
cc: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT, Steven K  
Davidsen/LAKE/PPRD/ABBOTT@ABBOTT  
Subject: ABT 518 Slides

Perry

Attached please find requested draft slides on MMP1 program including ASCO summary, program status,  
and program recommendation.

Minutes from the Friday ABT-627 DMC Project Review will be available tomorrow morning.

Bob



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ABBT 0033486



ABT 518 ASCO - Plan May 21, 2001.

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**ABBT 0033487**

# ASCO 2001 MMPI Update

- Ten MMPI abstracts were presented
- Prinomastat, marimastat & Bay 12-9566 reported negative findings

## Possible reasons

- Under dosing due to dose limiting toxicity (joint toxicity)
  - Inappropriate tumor selection
  - Inappropriate tumor stage (late vs. early)
  - Phase II development not done for prinomastat & Bay 12-9566
- BMS 275291 did not show joint toxicity in Phase I. Phase II studies are being initiated in NSCLC & Kaposi's sarcoma

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ABBT 0033488

# Prinomastat

- Non-small cell lung cancer
  - Combination with paclitaxel & carboplatin
  - No survival benefit
- Hormone refractory prostate cancer
  - Combination with mitoxantrone & prednisone
  - No effects on: PSA, progression free survival, overall survival
- Refractory metastatic breast cancer
  - Phase I/II single agent (n = 44)
- Grade 2 joint toxicity in above trials at all dose levels (5,10,25 mg bid)
- Studies in earlier stage tumors are still ongoing

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ABBT 0033489

# Marimastat

- Small cell lung cancer
  - Following response to 1<sup>st</sup> line therapy
  - 10mg vs. placebo
  - Total 155 patients
  - No benefit on progression free survival or overall survival
- Glioblastoma
  - Post surgery & radiotherapy
  - 10mg vs. placebo
  - Total 162 patients
- High dropout rate due to joint toxicity

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ABBT 0033490

## Bay 12-9566

- Ovarian cancer (stage III or IV)
  - 800mg bid vs. placebo
  - Study was discontinued prior to full enrollment due to lack of activity in pancreatic cancer and SCLC
  - No benefit on survival

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ABBT 0033491

## BMS 275291

- Phase I studies
  - Healthy volunteers (n = 40 males)
  - Cancer patients (n = 44)
- No joint toxicities (possibly due to lack of sheddase activity)
- No MTD through 2400mg / day
- Phase II plan
  - Non small cell lung cancer in combination with paclitaxel & carboplatin
  - Kaposi's sarcoma
  - Dose 1200 mg / day

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ABBT 0033492

# ABT-518 Phase I Multiple-Dose Study in Cancer Patients M00-235

- Patients enrolled to date
  - 25 mg / day 4
  - 50 mg / day 3
- Dosing duration up to 57 days
- Patients will continue dosing until disease progression or adverse events
- No musculoskeletal effects reported to date
- Next dose is 100 mg / day

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ABBT 0033493



# ABT-518 Development

## Recommendations

- Continue the ongoing Phase I study
  - Objectives
    - Determine target dose required to achieve target plasma concentration of 1-3  $\lambda$ M
    - Assess safety following chronic administration
- Stop development if Grade 3 or 4 toxicities are attributed to doses at or below target dose
- Stop for joint toxicity
- If target dose is well tolerated, initiate a pharmacodynamic/proof of principle study with external funds (e.g., NCI-CRADA) and/or outlicense
  - Biopsy multiple melanoma, head and neck cancer, assay for gelatinase A/B activity

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ABBT 0033494

40

## **Deposition Exhibit No. 40**

**D's Exhibit 833**



Perry D Nisen  
06/11/2001 01:25 PM

To: Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
cc:  
Subject: Re: MMPI data from subject "X" (additional info)

Damn right.  
Steven K Davidsen

Steven K Davidsen  
06/11/01 03:24 PM

To: Perry D Nisen/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: Re: MMPI data from subject "X" (additional info)

Perry,

This data ain't bad.... damn near target exposure with 25 mg dose. Metabolites are low at 22 days, no apparent induction of metabolism. Independent of whether ABT-518 is pursued further, I think it's safe to say that the decision to take it into clinical studies was not stupid....

Steve  
Perry D Nisen



Perry D Nisen  
06/10/01 10:17 PM

To: Steven K Davidsen/LAKE/PPRD/ABBOTT@ABBOTT  
cc:  
Subject: MMPI data from subject "X" (additional info)

----- Forwarded by Perry D Nisen/LAKE/PPRD/ABBOTT on 06/10/01 10:17 PM -----



Azmi A Nabulsi  
06/09/01 10:18 PM

To: Perry Nisen, steven davidsen  
cc:  
Subject: MMPI data from subject "X" (additional info)

FYI. These are quick calculations that I asked Bob to do once we received the data for on Friday. As you will see, it does not look bad for a 25 mg dose.

Azmi

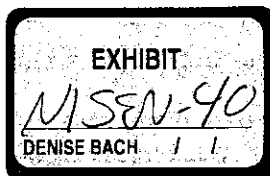
----- Forwarded by Azmi A Nabulsi/LAKE/PPRD/ABBOTT on 06/09/01 10:14 PM -----

Robert A Carr  
06/08/01 05:01 PM

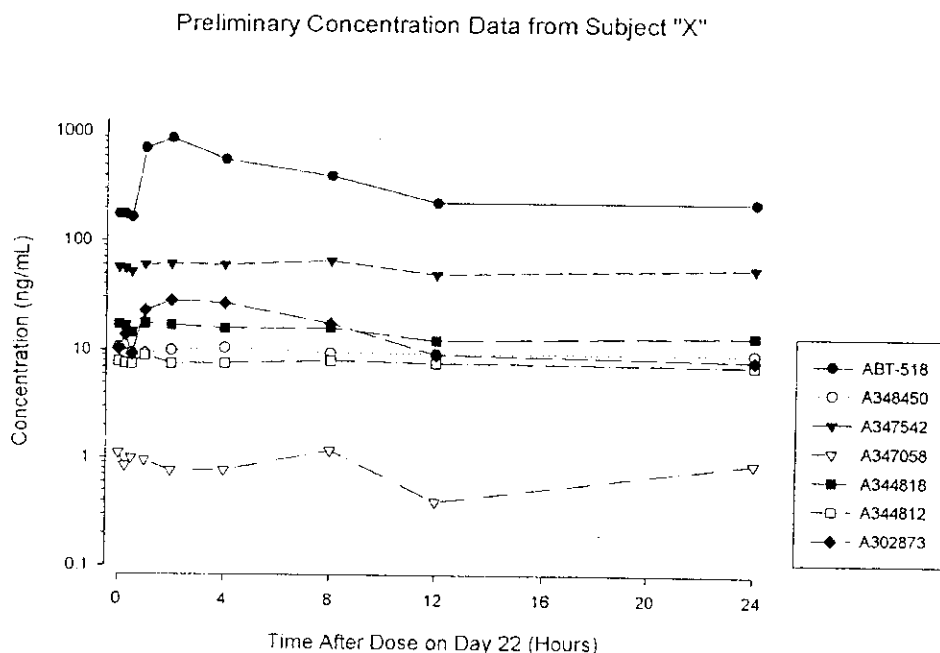
To: Azmi A Nabulsi/LAKE/PPRD/ABBOTT@ABBOTT  
cc: Walid Awni/LAKE/PPRD/ABBOTT@ABBOTT  
Subject: MMPI data from subject "X" (additional info)

Azmi,

I believe this subject received 25 mg ABT-518 QD. Following is a plot of parent drug and metabolite concentrations over a 24-hour dosing interval following the dose on Day 22.



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ABBT0063625



As stated in the transition strategy document (August 2000), if targeted trough concentrations of 100 ng/mL cannot be achieved with oral dosing of ABT-518, or if either an excessive dose (>2 grams) or dosing frequency (more than BID) is required, a No Go recommendation will be made.

The data shown above from one subject indicate that the pharmacokinetic targets for this compound can be met. In this subject, a dose of 25 mg QD achieved trough concentrations of about 200 ng/mL. Steady-state concentrations ranged from about 200 to 900 ng/mL. Metabolite concentrations were very low relative to parent drug. Ratios of AUCs (metabolite to parent) were less than 5%, except for A347542 (16%). Metabolite concentrations appeared to substantially achieve steady state by Day 22.

In mouse efficacy studies, AUC<sub>24</sub> values of 2.6 and 22 mcg·h/mL were effective in B16 and HT1080 models, respectively. The AUC<sub>24</sub> for Subject "X" was 8.4 mcg·h/mL.

Bob